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Synthetic Studies on Diarylheptanoids and Diterpenes

Synthetic Studies on Diarylheptanoids and Diterpenes

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A thesis submitted to the University of Bristol as part of the requirements for award of the degree of Doctor of Philosophy in the Faculty of Science

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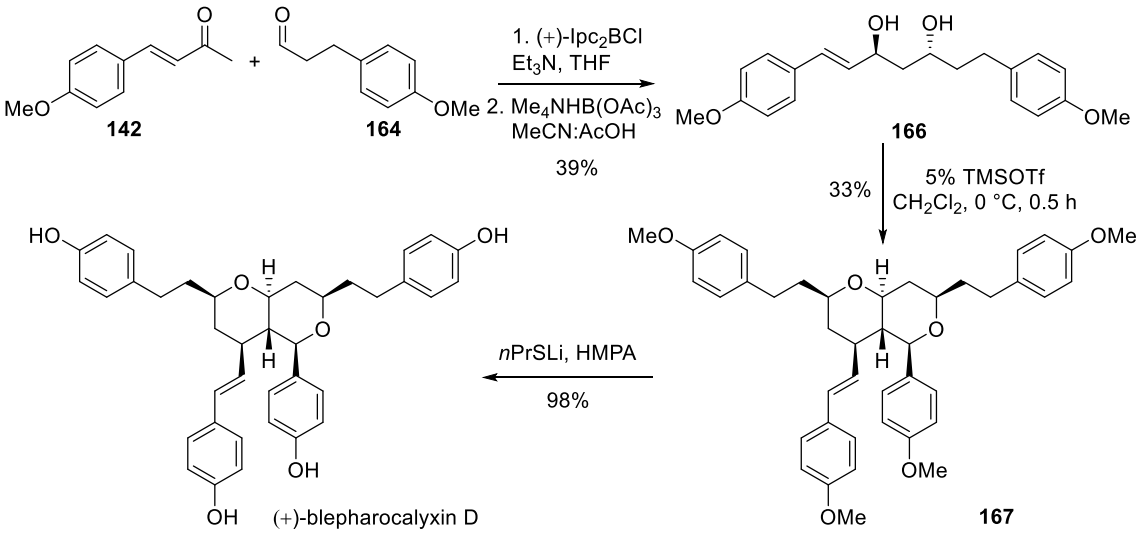
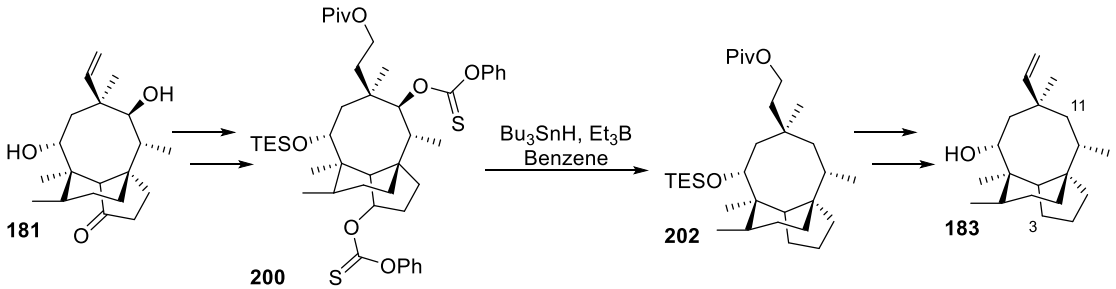
Abstract

This thesis describes the development of a bioinspired approach for the efficient synthesis of bicyclic heterocycles assembled on a 2,8-dioxabicyclo[4.4.0]decane core decorated with 4 side chains. The key step involves an acid mediated dimerisation of a linear dihydroxy-diarylheptanoid to produce two oxane rings and 4 stereocenters in one pot. This route was used for the total synthesis of (+)-blepharocalyxin D in 4 steps and 13% overall yield from simple starting materials. Further analogues were also synthesised.



The conditions for the key dimerisation step were optimised in terms of temperature, Lewis acid and solvent, concluding in the use of TMSOTf in CH_2Cl_2 at 0 °C. A mechanism for the reaction was proposed via a cascade involving carbocationic intermediates and verified by an oxygen-18 label study.

The second chapter describes the synthesis of 3-deoxo-11-dehydroxy-mutilin **183** the first cyclic intermediate on the biosynthetic pathway to pleuromutilin. It was used as a standard to verify the structure of the metabolite isolated from extracts of cultures of *Aspergillus oryzae*, which has genes heterologously expressed from *C. passeckerianus*.



Acknowledgements

I would like to thank Professor Chris Willis for giving me the opportunity to become part of her research group and her supervision during my PhD. She was always there to listen and support me, not only with my project but also with any other circumstances and plans that arisen, including my future career. I am also grateful for all the time she spent on teaching me, her immense patience and endless encouragement that have made this work possible.

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A very special thank goes to Erzsebet Thornberry and Yasmin Godage for their great support with the HPLC. I really appreciate the help on running samples, answering my multiple questions and for always find the way to make the instrument work. Also, many thanks to the rest of the technical staff at the School of Chemistry to keep all the instrumentation up and running and helping whenever I required.

A very big thank you to the Willis group (past and present) for making my time in the lab unforgettable. A particular thanks go to Alex (Li-Chen Han) who literally was always by my side, for his company when working early mornings and late evenings, for his teaching and encouragement, for those endless chats and for being a really good friend all along. Thanks also to Nick and Hanim (who completed the early morning quartet, for the countless laughs and many coffee trips), Luoyi (for the nice chats and for never refusing to help me), David, Paul (for always caring and looking after me), Dan (for being such a great roommate), Akrill (for introducing me to the lab and being so patience), Lisa (for organising so many great events), Jon, Joe, Abby (for always knowing when an ice cream was required), Angus (for the daily jokes), Kun, Sbu and the youngest gang that I didn't have the pleasure to know better, Jawaher, Andrew, Bin and James.

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Author's Declaration

The work described in this thesis was carried out in the School of Chemistry, University of Bristol under the supervision of Professor C. L. Willis between September 2014 and September 2018. The work is original except where indicated by reference and has not been submitted for any other degree. The views expressed are those of the author and in no way represent those of the University of Bristol.

Edith Rodriguez Venegas

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Abbreviations

α_D^{25}	– specific optical rotation at 25 °C
Ac	– acetate
BINOL	– 1,1'-bi-2-naphthol
br	– broad
cDNA	– complementary DNA
d	– doublet
DIBALH	– diisobutylaluminium hydride
DIPEA	– diisopropylethylamine
DMAP	– *N*,*N*-dimethylaminopyridine
DMF	– *N*,*N*-dimethylformamide
DMSO	– dimethyl sulfoxide
dr	– diastereomeric ratio
ED_{50}	– effective dose for 50% of the patient base
er	– enantiomeric ratio
ESI	– electrospray ionisation
FT-IR	– Fourier Transform Infrared
g	– gram
GII	– Grubbs' catalyst 2nd generation
hept	– heptet
HMPA	– hexamethylphosphoramide
HPLC	– high performance liquid chromatography
HRMS	– high resolution mass spectrometry
HSQC	– heteronuclear single-quantum spectroscopy
HWE	– Horner-Wadsworth-Emmons
Hz	– Hertz
IC_{50}	– inhibitory concentration
Ipc	– isopinocampheyl
LDA	– lithium diisopropylamide
LiHMDS	– lithium hexamethyldisilazide
M	– molar
MHz	– Mega Hertz
ml	– millilitre
mM	– millimolar
mmol	– millimole

mp	– melting point
Ms	– methanesulfonyl
NaHMDS	– sodium bis(trimethylsilyl)amide
NMR	– nuclear magnetic resonance
nOe	– nuclear Overhauser effect
Nu	– nucleophile
ORD	– optical rotatory
pent	– pentet
pKa	– acid dissociation constant
pTSA	– *p*-toluenesulfonic acid
py	– pyridine
q	– quartet
s	– singlet
spt	– septet
t	– triplet
TBAF	– *tert*-butylammonium fluoride
TBS	– *tert*-butyldimethylsilyl
TES	– triethylsilyl
Tf	– triflate
TFA	– trifluoroacetic acid
THF	– tetrahydrofuran
THP	– tetrahydropyran
TLC	– thin layer chromatography
TMEDA	– tetramethylethylenediamine
TMS	– trimethylsilyl
Ts	– *p*-toluenesulfonyl
UV	– ultraviolet
w/v	– weight per volume

Table of Contents

1. A Bioinspired Strategy for the Synthesis of Fused Oxygen Heterocycles.

1.1 Introduction

1.1.1 Natural products in drug discovery and their bioinspired synthesis

Natural products have been the single most productive source of leads for the development of drugs. In 2008, over 100 new natural products were in clinical development, particularly as anti-cancer and anti-infectives.[1] Natural products are generally compliant in terms of log *P* and H-bond donors, even if they violate the Lipinski's rule of five[2], making them often more readily absorbed than synthetic drugs. In addition, natural products are more likely to resemble biosynthetic intermediates or endogenous metabolites, and hence take advantage of active transport mechanisms.[3] Despite these advantages and the past successes, many large pharmaceutical companies have decreased the use of natural products in drug discovery screening. This has been because of the potential disadvantages of natural products such as difficulties in access and supply due to the complexities of natural products chemistry.[1] Although several strategies are used in the commercial production of natural products including fermentation, biotransformation, total synthesis and semi-synthesis, it is important to develop efficient new synthetic methodology.

The use of bioinspired or biomimetic synthesis has grown in recent years,[4] this attempts to mimic nature's processes for the synthesis of natural occurring metabolites, drawing on the knowledge of known or proposed biosynthetic steps. In this type of synthesis key transformations are used to convert simple precursor into complex molecules often through highly orchestrated cascades.[4]

In this chapter a bioinspired strategy for the direct conversion of monomeric 3,5-dihydroxy-diarylheptanoids to dimeric products assembled on a *trans*-2,8-dioxabicyclo[4.4.0]decane frameworks is described alongside oxygen-18 and deuterium labelling studies to verify a proposed cascade mechanism involving carbocationic intermediates and the concise total synthesis of blepharocalyxin D analogues.

1.1.2 Isolation, structure elucidation and bioactivities of diarylheptanoids from *Alpinia blepharocalyx*

Alpinia blepharocalyx K. Schum belongs to the large genus of the Zingiberaceae family which consists of over 250 species of which about 50 species are distributed in East and South-West China. Extracts of *A. blepharocalyx* K. Schum have been used as Traditional Chinese Medicine for the treatment of stomach disorders. Phytochemical studies of this plant have resulted in the isolation of diarylheptanoids, terpenes and many other compounds.[5]

Diarylheptanoids are classified into 5 characteristic subtypes: linear (e.g. **1**), cyclic (e.g. **2**), dimeric (e.g. **3**), those containing a chalcone/flavanone moiety (e.g. **4**) and further miscellaneous diarylheptanoids (Figure 1). All these compounds have the same characteristic skeleton of two aromatic rings joined by a 7-carbon atom chain.[6]

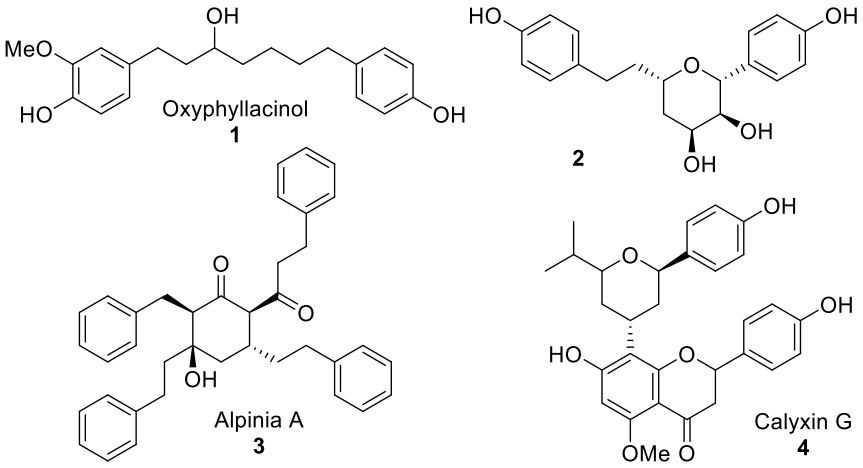


Figure 1. Examples of diarylheptanoids isolated from *A. blepharocalyx*

In 1998, in order to find the biologically active compounds, seeds of *A. blepharocalyx* were extracted with 95% EtOH, and the EtOH extract was suspended in water containing 10% MeOH and partitioned with hexane and Et_2O.[7] Linear diarylheptanoid **5** (32 mg) was one of the first isolated compounds. Its formula $C_{19}H_{18}O_4$ (M^+ 310.1183) was determined by HRMS and was positive to $FeCl_3$ reagent, so it was suggested to be the enol form of a 1,3-diketone. Using IR and extensive 1D and 2D NMR spectroscopy the structure of compound **5** was determined. Its antiplatelet activity was assessed and showed strong inhibition in platelet aggregation induced by collagen, arachidonic acid and adenosine diphosphate (Figure 2).[7]

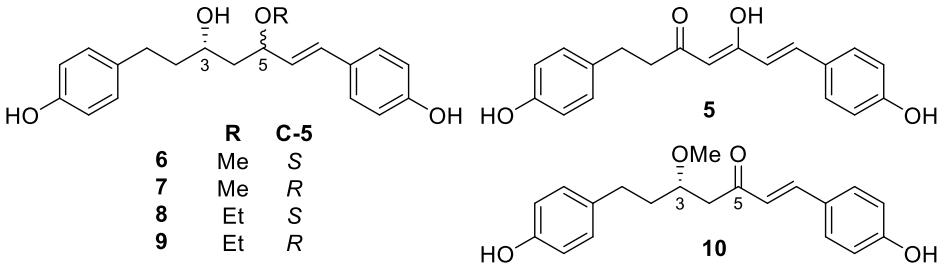


Figure 2. Linear diarylheptanoids isolated for *A. blepharocalyx*[7]

A few years later in 2001 it was reported that the diethyl ether and residual aqueous fractions from the EtOH extract of seed of *A. blepharocalyx* showed significant antiproliferative activity against liver metastatic murine colon 26-L5 carcinoma cells[8] and human HT-1080 fibrosarcoma cells;[9] hence, these fractions were further examined. The residual aqueous fraction was separated by a series of chromatographic methods and the linear diarylheptanoids (**6**-**10**), diarylheptanoids bearing a chalcone or a flavanone moiety (**11**-**14**), cyclic (**15** & **16**) and dimeric (**17**-**19**) diarylheptanoids were isolated. Their structures were determined by HRMS, IR and extensive ^{1}H and ^{13}C NMR spectroscopy.

Linear diarylheptanoids **6** (3.2 mg) and **7** (3.9 mg) contain a methoxy group at C-5. Their absolute stereochemistry was assigned by analyses of their MTPA derivatives using Mosher's method.[10] Compounds **8** (2 mg) and **9** (2 mg) have an ethoxy group at C-5 instead of the methoxy group. Their absolute configurations were assumed based on comparison with **6** and **7** and that all have positive optical rotation. β-Methoxy ketone **10** (2.5 mg) was also isolated and its configuration at C-3 was assumed to be the same as **6**-**9** (Figure 2).[11]

Among the diarylheptanoids bearing a chalcone or a flavanone moiety, calyxin I (**11**) (18.6 mg), epicalyxin I (**12**) (4.0 mg) , calyxin J (**13**) (18.3 mg) and an epimeric mixture (18.2 mg) of calyxin J (**13**) and epicalyxin J (**14**) were also isolated (Figure 3).

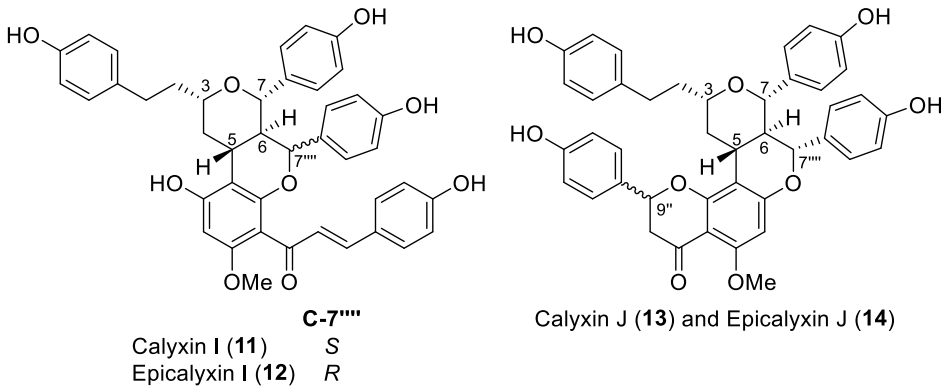


Figure 3. Diarylheptanoids containing a chalcone or flavanone moiety isolated from *A. blepharocalyx*[12]

Calyxin I (**11**) and epicalyxin I (**12**) contain a chalcone moiety and were assumed to be epimers at C-7'''' based on the similarity on their ^{1}H and ^{13}C spectra and because the coupling constant between H-6 and H-7'''' in **12** (*J* 4 Hz) differed from that of **11** (*J* 10 Hz).[12] Calyxin J (**13**) and epicalyxin J (**14**) contain a flavanone moiety[13] and they were assigned as epimers at C-9'' although this stereochemistry could not be determined due to the paucity of **13** and **14** available.[12] The structures of several related calyxin natural products originally assigned by Kadota, were reassigned by Rychnovsky following total synthesis.[14]

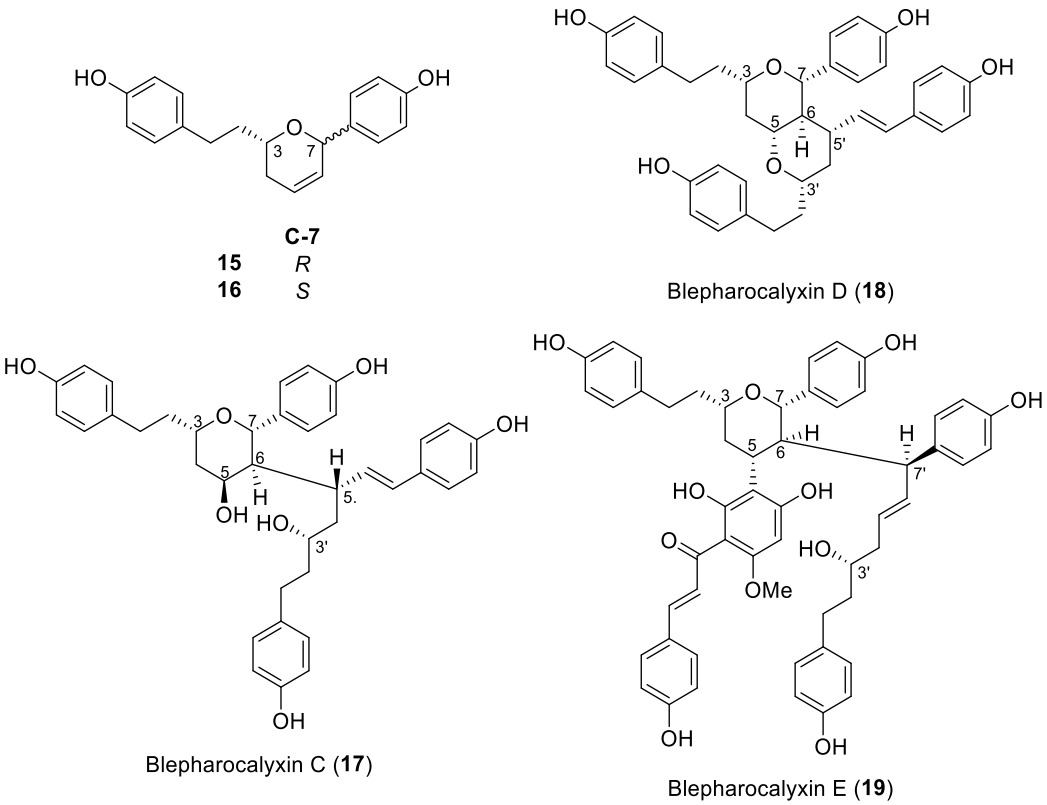
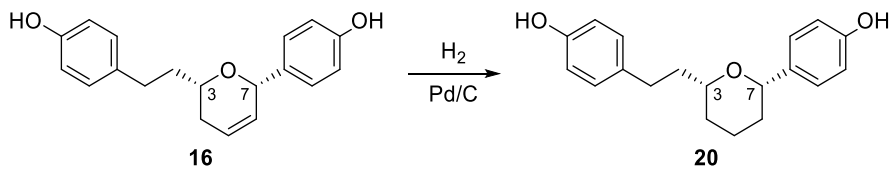


Figure 4. Cyclic and dimeric diarylheptanoids isolated from *A. blepharocalyx*[15]

Cyclic diarylheptanoids such as **15** and its epimer **16** and dimeric diarylheptanoids including blepharocalyxins C (**17**), D (**18**) and E (**19**) were also isolated (Figure 4). The structure of dihydropyran **16** (1.4 mg) was verified *via* hydrogenation with Pd/C catalyst to give the known diarylheptanoid (–)-de-*O*-methylcentrolobin (**20**)[16–18] (Scheme 1) which has been synthesised several times.[19–21]



Scheme 1. Hydrogenation of dihydropyran **16** to (–)-de-*O*-methylcentrolobin **20**[18]

Dihydropyran **15** (7.1 mg) was assumed to be an epimer of **16** at C-7 based on the similarity of its ^{1}H and ^{13}C NMR spectra. As the configuration at C-3 was assumed to be *S* from the biogenetic point of view,[22] the absolute configuration of **15** was determined as 3*S*, 7*R*.[15]

Dimeric diarylheptanoids blepharocalyxin C (**17**) (5.8 mg) and blepharocalyxin D (5.5 mg) (**18**) were also isolated. Blepharocalyxin D has a similar structure to blepharocalyxin C except that ring closure had occurred to form a second oxane ring. Blepharocalyxin E (**19**) (7.0 mg) has the two diarylheptanoids coupled *via* the 6-7' bond as shown in Figure 4.[22]

The antiproliferative activity of these compounds **6**-**19** against liver metastatic murine colon 26-L5 carcinoma cells and human HT-1080 fibrosarcoma cells was tested and compared with 5-fluorouracil, a current medication used to treat cancer.[23] Their ED_{50} values (median effective dose, the concentration of drug at which 50% of the population will have the desired response[24]) are shown in Table 1.

Compound	Colon 26-L5	HT-1080
6	86.4	>100
8	94.6	>100
10	5.2	10.1
Calyxin I (**11**)	8.39	9.08
Epycalyxin I (**12**)	12.1	5.88
Calyxin J (**13**)	23.2	8.19
calyxin J (**13**) and epicalyxin J (**14**)	13.7	0.32
15	71.2	45.3
16	>100	79.4
Blepharocalyxin C (**17**)	29.6	54.3
Blepharocalyxin D (**18**)	3.61	25.7
Blepharocalyxin E (**19**)	32.2	9.02
5-fluorouracil	0.5	8.0

Table 1. Antiproliferative activity for compounds **6**-**19** and 5-fluorouracil (ED_{50} values in μM) [11,12]

Linear diarylheptanoids **7** and **9** were inactive (ED_{50} > 100 μM) in both cells, whereas **6** and **8** showed antiproliferative activity only towards human fibrosarcoma cells and compound **10** showed cytotoxicity against both cell lines.[11] Calyxins **11**-**14** showed moderate to potent cytotoxicity against human fibrosarcoma cells with ED_{50} values less than 10 μM.[12]

Blepharocalyxin D (**18**) showed the most potent antiproliferative activity against murine colon carcinoma cells with an ED_{50} value of 3.61 μM, which falls within the range of significantly active cytotoxic agent (ED_{50} < 4.0 μM) introduced by Geran *et al*.[25] Blepharocalyxin E (**19**) exhibited the most potent activity against human fibrosarcoma cells with a ED_{50} value of 9.02 μM, which is comparable with that of 5-fluorouracil (ED_{50} 8.0 μM).[22,26]

1.1.3 Previous synthetic studies and total syntheses of blepharocalyxin D

A characteristic feature of blepharocalyxin D is the unusual *trans*-2,8-dioxabicyclo[4.4.0]decane central core which is adorned by four side chains each in an equatorial position (Figure 5). Its structure was assigned by Kadota and co-workers in 2000 based on ^{1}H and ^{13}C NMR spectroscopic data and its stereochemistry determined as 1*R*, 3*S*, 5*S*, 6*S*, 7*S*, 9*S* by comparison with blepharocalyxin C which was reported at the same time.[22,26]

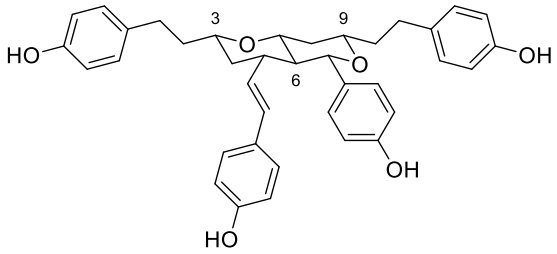
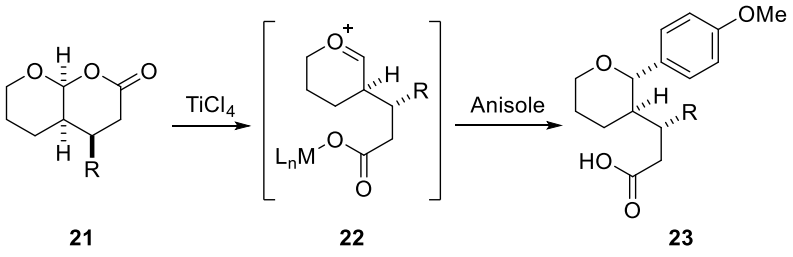


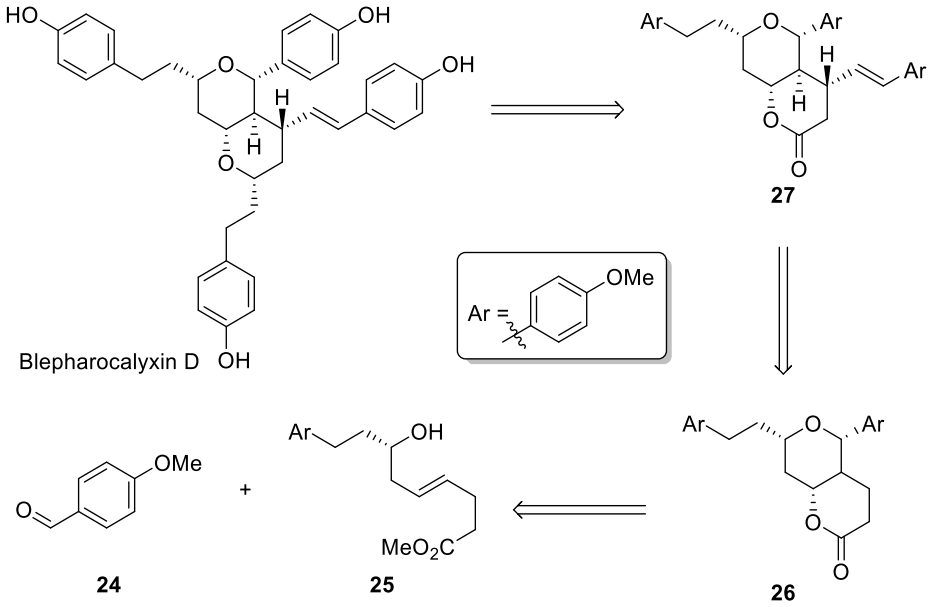
Figure 5. 3D representation of blepharocalyxin D (**18**)

The interesting structure of blepharocalyxin D combined with its high cytotoxicity against murine colon carcinoma cells and the need for further material for biological assessment (only 5.5 mg was isolated from 10 Kg of seeds) led several research groups to investigate the total synthesis of this natural product. In 2003, Mead and co-workers[27] reported a ring cleavage strategy of model bicyclic lactones promoted by a Lewis acid. Cleavage of **21** using $TiCl_4$ generates an intermediate oxycarbenium ion **22** which can be captured by a variety of carbon-based nucleophiles. Mead found that anisole reacts only at the *para*-position to give the desired *trans* diequatorial C-aryl pyranoside product **23** (Scheme 2).



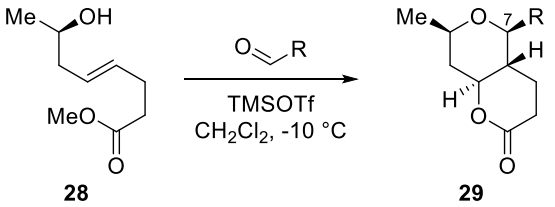
Scheme 2. Preparation of tetrahydropyran **23**[27]

Initial studies towards the synthesis of blepharocalyxin D within our group were begun by former PhD student, Jon Elsworth. The retrosynthetic plan *via* a Prins cyclisation is shown in Scheme 3. The key step involved the reaction of homoallylic alcohol **25,** containing a tethered ester, with aldehyde **24** to form **26**, the bicyclic scaffold of blepharocalyxin D in one step.[28]



Scheme 3. Retrosynthetic analysis of blepharocalyxin D[28]

Elsworth conducted model studies to investigate this novel cyclisation. Hydroxy ester **28** was synthesised and reacted with various aldehydes and a ketone in the presence of TMSOTf giving the required bicyclic framework **29** in good yields. In each case the reaction proceeded with excellent stereocontrol forming 3 new stereogenic centres in a single pot and a variety of groups could be introduced at C-7 including electron-rich and electron-deficient aromatic rings, alkyl side chains and a cyclopentane group (Table 2).[29]



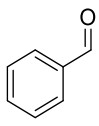
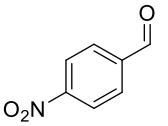
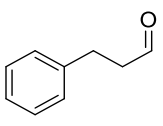
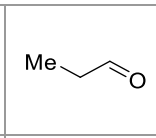
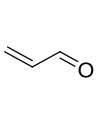
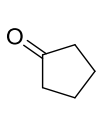
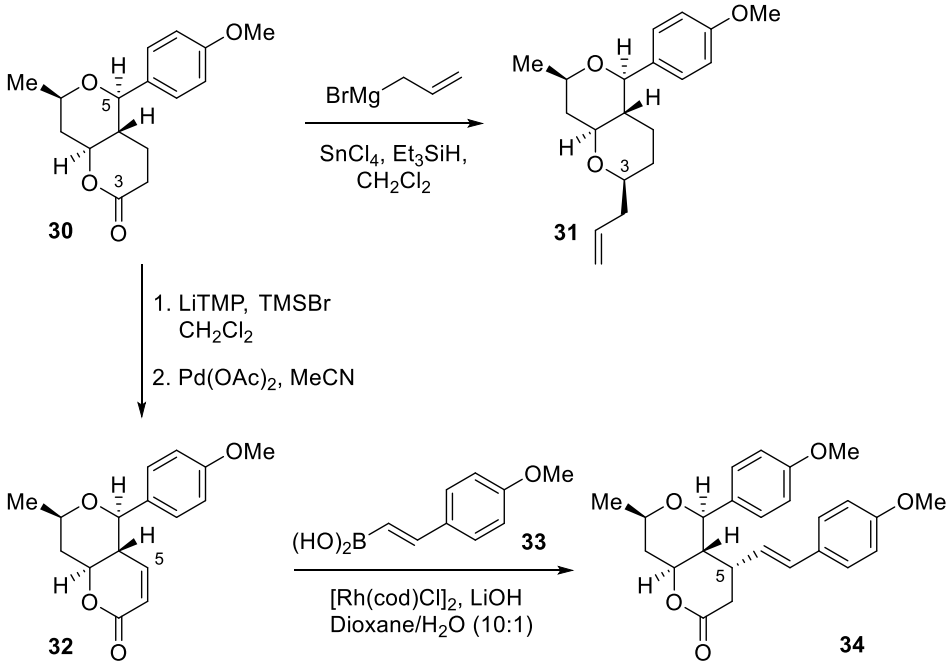
Electrophile						
Yield (%)	81	71	73	72	84	63

Table 2. Reaction of alcohol **28** with a range of electrophiles[29]

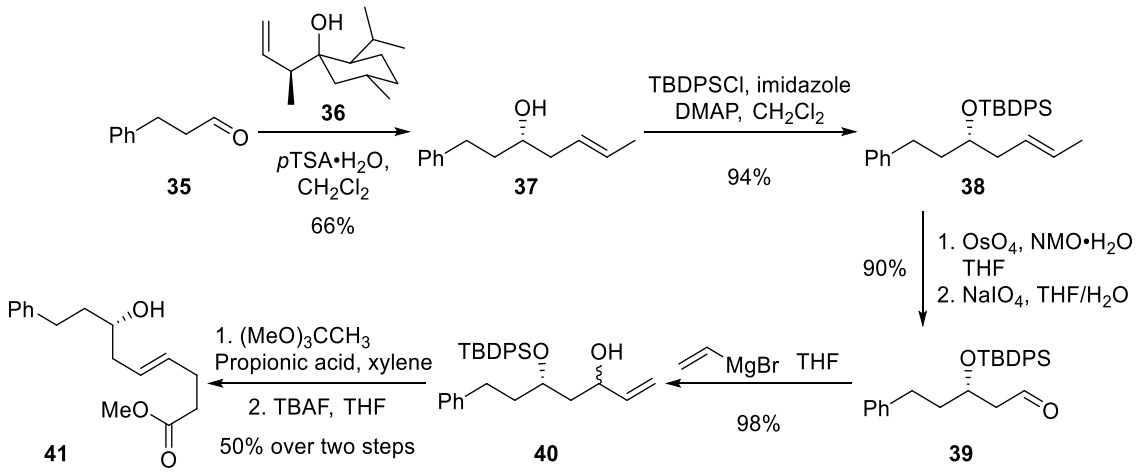
Having developed this novel intramolecular Prins cyclisation, Elsworth then explored the installation of the side chains which adorn blepharocalyxin D. He successfully introduced an alkyl chain at C-3 using a Grignard addition and subsequent stereoselective reduction using $SnCl_4$ and Et_3SiH to give **31** (Scheme 4).

The installation of the side chain at C-5 proved to be more challenging. Lactone **30** was treated with lithium tetramethylpiperidide (LiTMP) and trimethylsilyl bromide, subsequent Saegusa oxidation produced unsaturated lactone **32**. Treatment of **32** with boronic acid **33** in the presence of $[Rh(cod)Cl]_2$ and lithium hydroxide in a 10:1 mixture of dioxane/water gave alkylated lactone **34** as a single diastereomer in 91% yield (Scheme 4). However, product **34** had the opposite stereochemistry at C-5 to that required for the total synthesis of blepharocalyxin D.[28]



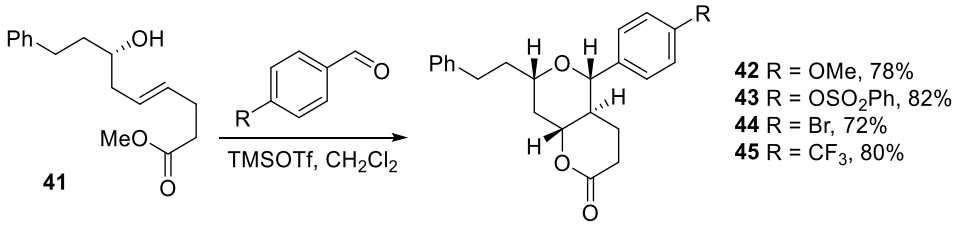
Scheme 4. Installation of side chains at C-3 and C-5[28]

With the model studies showing promise, a further PhD student within our group Tshepo Pheko synthesised unsaturated ester **41** with a phenylethyl side chain (Scheme 5). First, reaction of crotyl transfer reagent[30] **36** with dihydrocinnamaldehyde **35** in the presence of *p*TSA·H_2O in CH_2Cl_2 gave alcohol **37** in 66% yield and >98% *ee*. Protection of alcohol **37** and subsequent oxidative cleavage of the alkene gave aldehyde **39**. Reaction of vinylmagnesium bromide in THF with aldehyde **39** gave an epimeric mixture of alcohols **40**. Subsequent Johnson-Claisen rearrangement with trimethylorthoacetate and TBAF deprotection gave homoallylic alcohol **41**.[31]



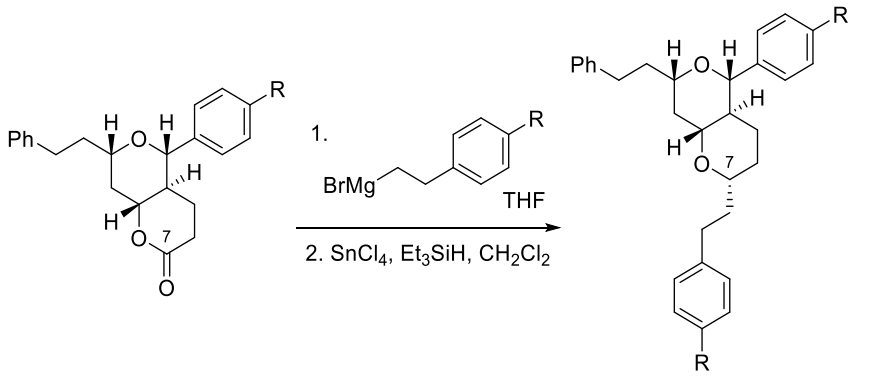
Scheme 5. Synthesis of homoallylic alcohol **41**[31]

Pheko treated homoallylic alcohol **41** and various aldehydes (differing in the *p*-substitution of the aromatic ring), with TMSOTf to give bicyclic lactones **42**-**45** in good yields and excellent stereoselectivities (Scheme 6).



Scheme 6. Synthesis lactones **42**-**45**[31]

The side chain at C-7 was installed using a two-step Grignard addition/reduction protocol in the presence of either an electron-donating (OMe) **46** or electron-withdrawing (OSO_2Ph) **47** substituent in the *para*-position of the aromatic ring (Scheme 7).

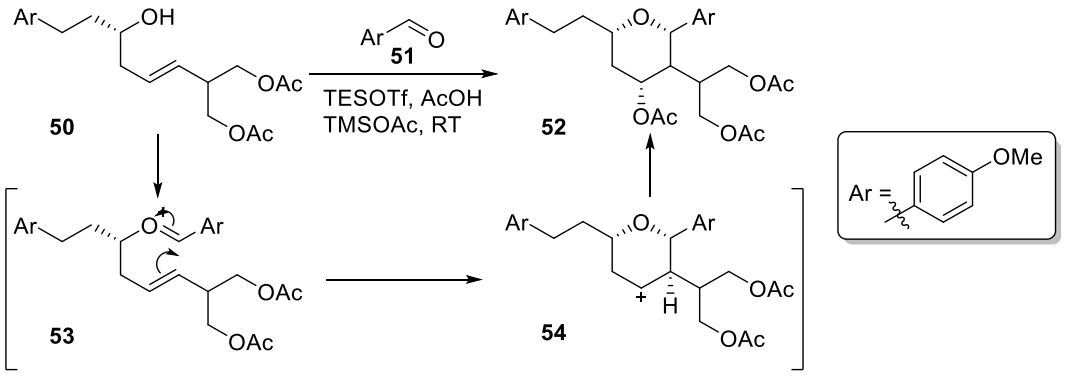


Scheme 7. Installation of side chain at C-7[31]

This had been good progress towards the synthesis of blepharocalyxin D, although the issue of obtaining the correct stereochemistry at C-5 remained.

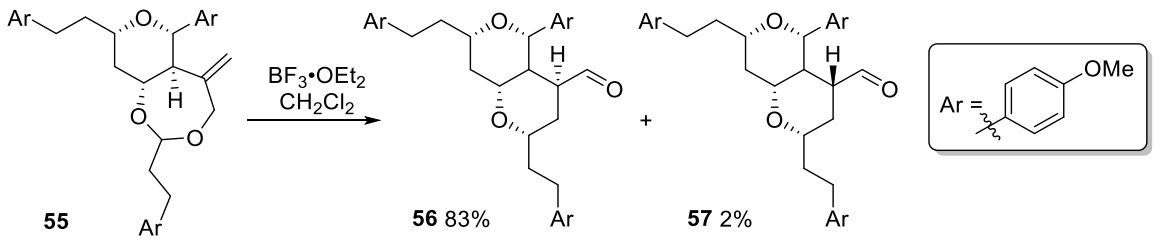
The first total synthesis of blepharocalyxin D was reported in 2007 by Lee and co-workers.[32,33] The synthesis was completed in 17 steps and 0.9% overall yield. The two keys steps included a Prins cyclisation and, an unusual Prins-pinacol rearrangement to form the two oxane rings.

The key Prins cyclisation of homoallylic alcohol **50** with *p*-anisaldehyde to produce tetrahydropyran **52** was performed under TMSOTf, TMSOAc and AcOH conditions, a modification of the Prins cyclisation conditions developed within our group[34] with creation of 3 new stereocenters. The mechanism of this Prins cyclisation is shown in Scheme 8. Homoallylic alcohol **50** reacts with aldehyde **51** to form intermediate oxycarbenium ion **53**, which cyclises to form stabilised secondary carbocation **54** which is trapped by a nucleophile to form the tetrahydropyran **52.**[35]



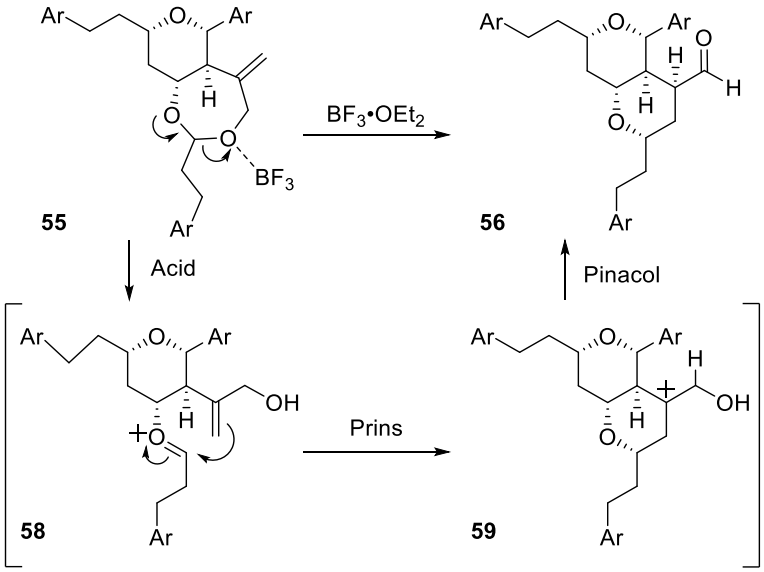
Scheme 8. Mechanism of the Prins cyclisation

The second key step is a Prins-pinacol rearrangement. Treatment of seven-membered cyclic acetal **55** with boron trifluoride diethyl etherate gave a mixture of the axial aldehyde **56** (83%) and the equatorial aldehyde **57** (2%) (Scheme 9). The authors propose that the unexpected preference for the axial aldehyde was due to conformational constraints originating from the steric crowding.



Scheme 9. Prins-pinacol rearrangement of **55** to give unexpected axial aldehyde **56**[32,33]

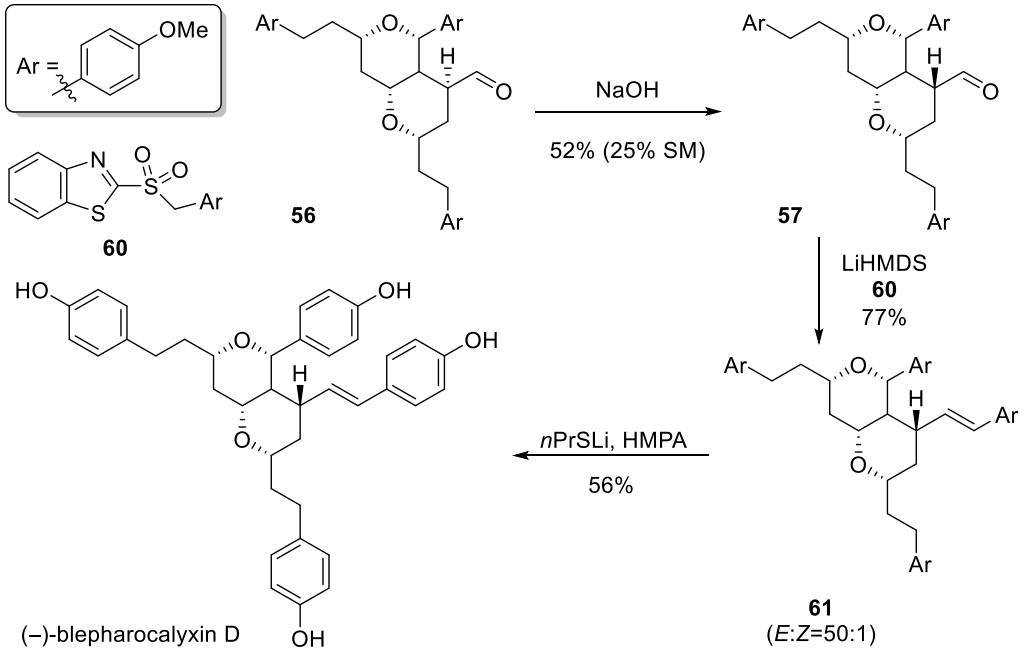
The proposed mechanism for this unusual Prins-pinacol reaction starts by activation of the most available oxygen of the seven-membered cyclic acetal **55** by the Lewis acid to form intermediate oxycarbenium ion **58**. The alkene attacks the activated carbonyl and forms the six-membered ring **59** in the Prins reaction, then pinacol rearrangement gives aldehyde **56** (Scheme 10).[36,37]



Scheme 10. Proposed mechanism of Prins-pinacol reaction

Epimerisation at C-5 of aldehyde **56** under basic conditions gave 52% of equatorial aldehyde **57** and 25% recovered starting material **56** which could be recycled to produce the desired aldehyde **57** (Scheme 11). The synthesis of blepharocalyxin D was completed *via* a Julia reaction[38] of lithiated sulfone **60** with aldehyde **57** and LiHMDS, giving tetramethyl ether **61** in 77% yield with a 50:1 *E*:*Z* ratio. The structure of **61** was confirmed by X-ray crystallography. Finally, **61** was demethylated using lithium propanethiolate in hot HMPA giving (–)-blepharocalyxin D (**18**) in 56% yield.

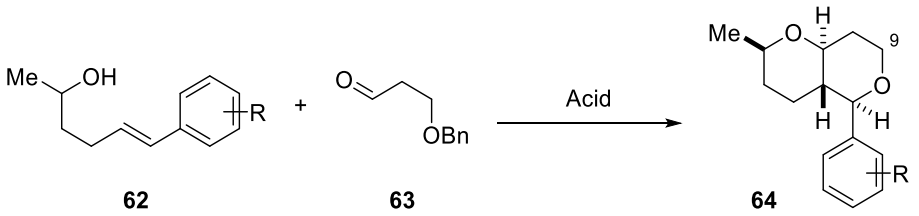
Lee reported several optical rotation values for blepharocalyxin D **18**: $[\alpha]_D^{22}$ –88.1 (*c*. 0.43, MeOH); $[\alpha]_D^{22}$ –77.1 (*c*. 0.11, MeOH); $[\alpha]_D^{22}$ –89.9 (*c*. 0.027, MeOH); $[\alpha]_D^{23}$ –72.9 (*c*. 0.32, acetone); $[\alpha]_D^{24}$ –85.0 (*c*. 0.31 MeOH-CH_2Cl_2 (1:1)).[33] These values were inconsistent with the values reported by Kadota and co-workers for the natural product:[22,26] $[\alpha]_D^{22}$ +18.5 (*c*. 0.025, MeOH). To confirm the structure beyond any doubt a synthetic sample of blepharocalyxin D **18** was converted back to the tetramethyl ether **61** using iodomethane and potassium carbonate in hot acetone. The optical rotation of this sample ($[\alpha]_D^{23}$ –87.8 (*c*. 0.065, $CHCl_3$)) was in close correspondence with the value of the original synthetic sample ($[\alpha]_D^{14}$ –90.4 (*c*. 0.32, $CHCl_3$)) of Blepharocalyxin D (**18**).



Scheme 11. Final steps in the synthesis of blepharocalyxin D[32,33]

It is interesting to note that both Lee and Elsworth obtained the axial substituent at C-5 in their approaches towards the synthesis of blepharocalyxin D, although in Lee's approach the aldehyde could be epimerised to the required equatorial position.

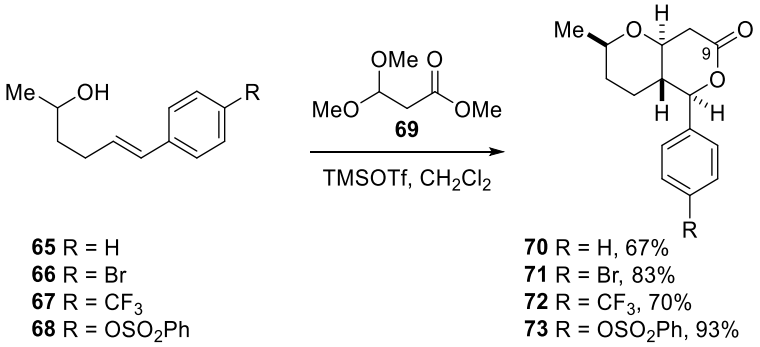
In 2012, Willis and co-workers reported a modification to the standard Prins cyclisation in which instead of using an homoallylic alcohol, a γ,δ-unsaturated alcohol was used. In this alcohol the alkene is placed one position further away generating a secondary carbocation which could be stabilised by an adjacent aromatic ring. Reaction of alkenols **62** with various functionalised aromatic groups (Cl, Br, CF_3 and OSO_2Ph) and 3-benzyloxypropanal **63** under Lewis acidic conditions afforded the *trans*-fused products **64** in good yields (Scheme 12).[39]



Scheme 12. Intramolecular Prins cyclisation to generate bicyclic compound **64**[39]

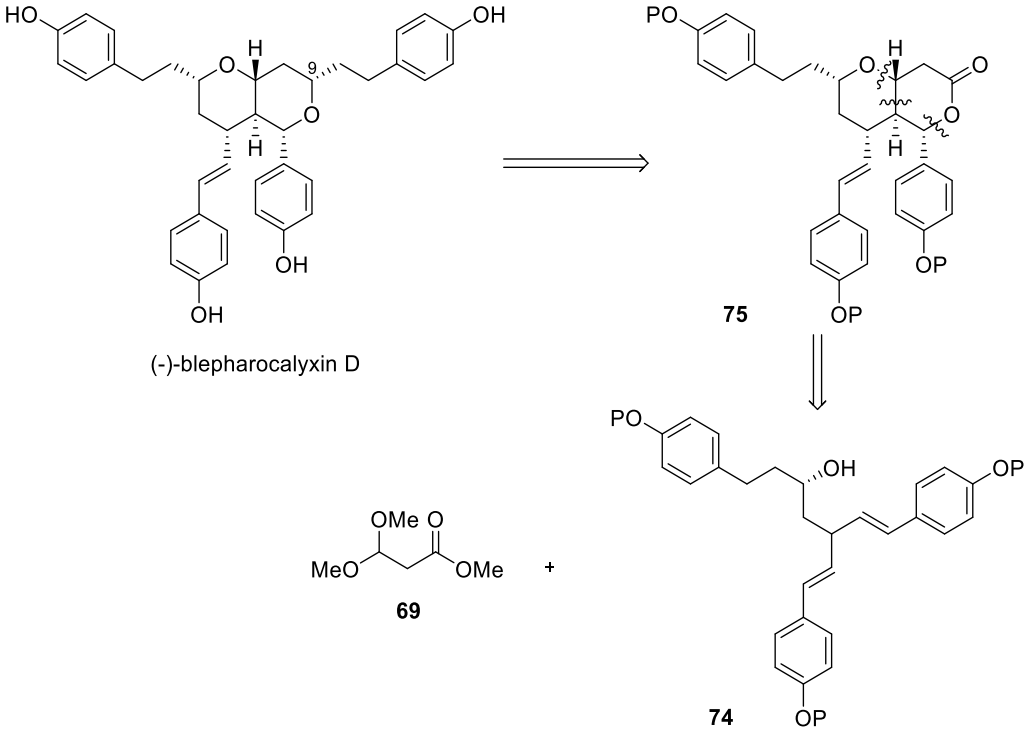
This was an efficient approach for the rapid stereocontrolled assembly of 2,8-dioxabicyclo[4.4.0]decanes, creating up to 3 new stereogenic centers in a single pot. Inconveniently, this method does not allow the introduction of a C-9 substituent requiring the synthesis of several functionalised alkenols and aldehydes prior to acid-mediated cyclisation.

Hence Adam Bunt, another former PhD student within the group, proposed that γ,δ-unsaturated alcohols could be used to generate bicyclic lactones with the carbonyl at C-9 to functionalise further.[40] Bunt achieved the synthesis of various bicyclic lactones **70**-**73** by reacting alcohols **65**-**68** and methyl 3,3-dimethoxypropionate **69** with TMSOTf to form the *trans*-fused bicyclic core (Scheme 13).



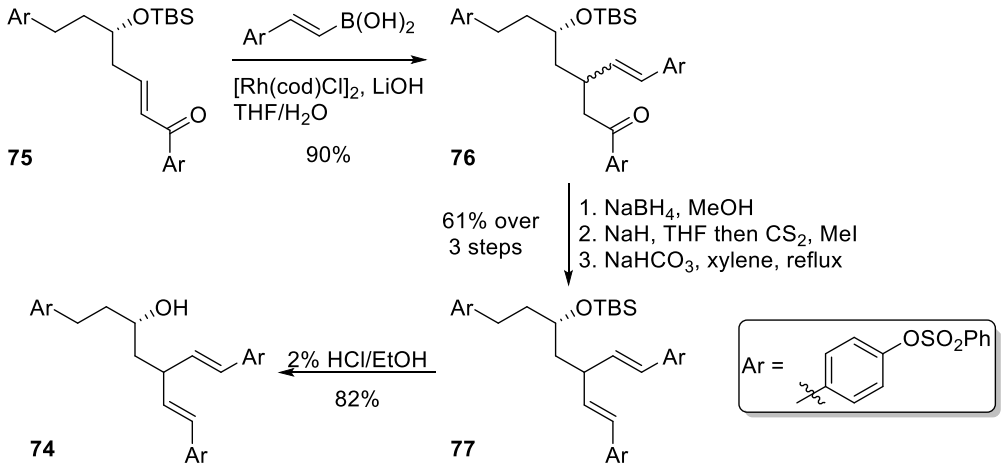
Scheme 13. Synthesis of bicyclic lactones **70**-**73**[40]

This new methodology paved the way for the development of a new approach for the total synthesis of blepharocalyxin D which was reported by Cons, Willis and co-workers[41] in 2013. The retrosynthetic analysis is showed in Scheme 14. The key step was proposed to be the reaction of dienol **74** with methyl 3,3-dimethylpropionate **69** to generate lactone **75** followed by installation of the required side chain at C-9.



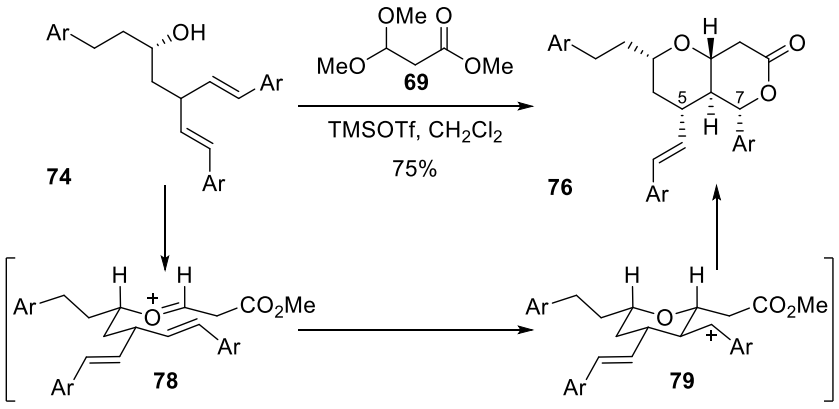
Scheme 14. New retrosynthetic analysis for the synthesis of blepharocalyxin D.

The required dienol **74** was synthesised from enone **75** which was converted to ketone **76** as a 1:1 mixture of diastereomers *via* a rhodium-mediated 1,4-addition reported by Hiyashi[42] (Scheme 15). Subsequent reduction with $NaBH_4$ gave corresponding benzylic alcohol which was converted to a xanthate using $NaH/CS_2/MeI$. The xanthate was refluxed with $NaHCO_3$ in xylene to effect a Chugaev elimination[43] giving the required alkene **77** in 61% yield. Silyl ether **77** was deprotected using 2% HCl in ethanol to give the required γ,δ-unsaturated alcohol **74**.[41]



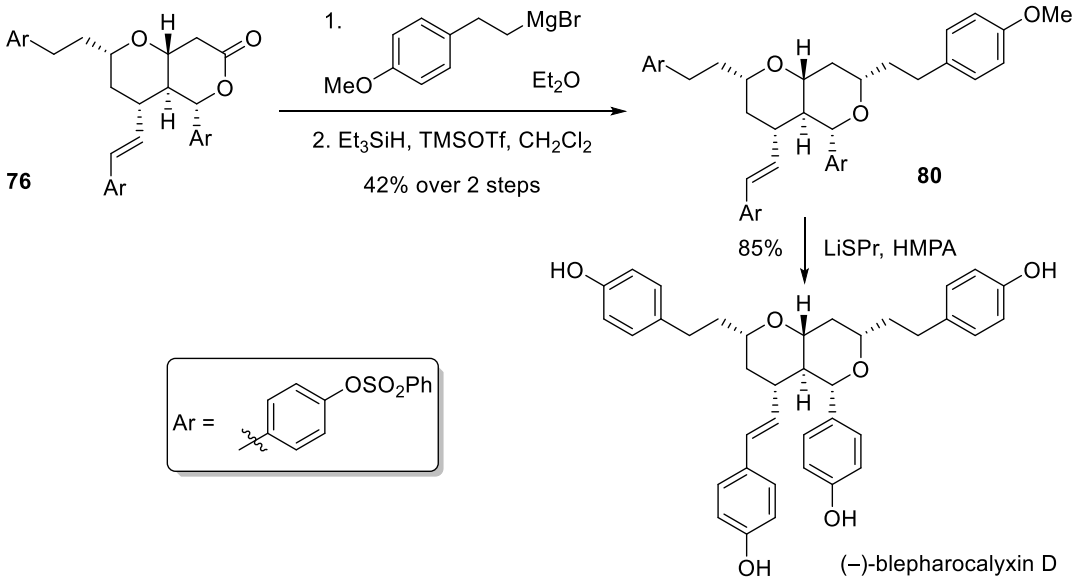
Scheme 15. Synthesis of dienol **74**[41]

With the required dienol **74** in hand, the key cyclisation was performed. Reaction of dienol **74** and ester **69** with TMSOTf gave bicyclic lactone **76** as a single diastereomer with the creation of two oxane rings and four stereocenters in 75% yield (Scheme 16). When dienol **74** reacts with ester **69,** in the presence of a Lewis acid, it generates an intermediate oxycarbenium ion **78**. Cyclisation gives stabilised carbocation **79** containing the first of the oxane rings with an equatorial substituent at C-5. Intramolecular trapping of the carbocation with the ester generates the second heterocycle giving lactone **76** with an equatorial substituent at C-7 (Scheme 16).



Scheme 16. Mechanism of the key cyclisation.

To complete the total synthesis, treatment of lactone **76** with 2-(*p*-methoxyphenyl)ethyl-magnesium bromide followed by reduction of the resultant lactol with TMSOTf and Et_3SiH gave **80** with the fully assembled carbon framework. Finally, deprotection of the phenolic groups with LiSPr/HMPA gave (−)-blepharocalyxin D in 8% overall yield after 15 steps (Scheme 17). The optical rotation of the synthetic sample $[\alpha]_D^{25}$ −79.2 (*c*. 0.23, MeOH) was in accord with Kadota's data.[33]



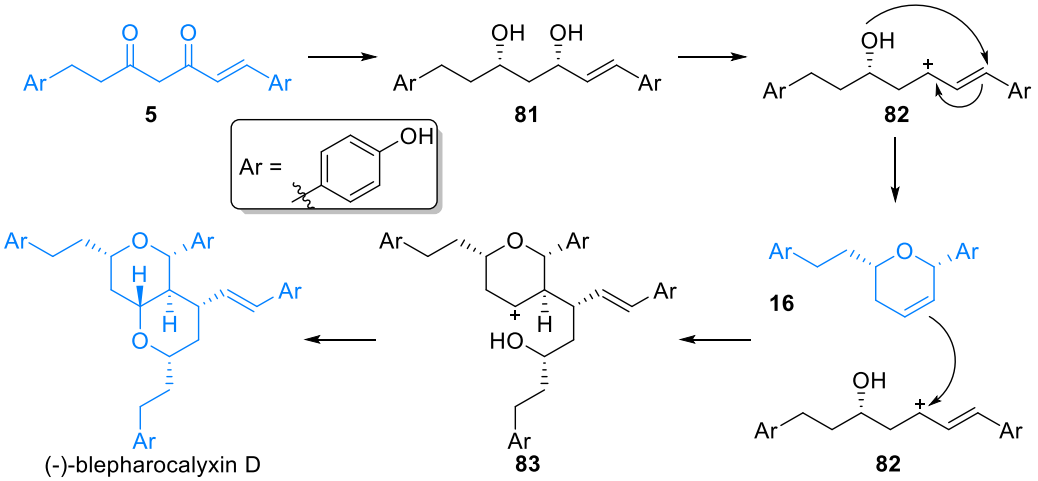
Scheme 17. Completing the synthesis of blepharocalyxin D[41]

1.2 Aim of the Project

This total synthesis is not easily adaptable for the preparation of analogues of blepharocalyxin D, as three of the side chains must be installed on the dienol used in the cyclisation step. With this in mind, a bioinspired strategy towards the synthesis of blepharocalyxin D was investigated.

Whilst no biosynthetic studies have been reported for these diarylheptanoids, Kadota and co-workers speculated on their possible biogenesis based on co-metabolites isolated from *A. blepharocalyx*.[22] They proposed that loss of water from dihydroxy-diarylheptanoid **81** would give allylic carbocation **82**. Intramolecular attack of the C-3 hydroxyl group to the benzylic (C-7) carbocation could cyclise to dihydropyran **16** (Scheme 18). Reaction of **16** with another molecule of carbocation **82** may give the dimeric structure **83**. The secondary carbocation on **83** could then be subject to a final intramolecular attack by the secondary alcohol to form the second

oxane ring of blepharocalyxin D. Thus, this was the starting point for our investigations on the development of a concise new approach to the synthesis of dimeric diarylheptanoids.



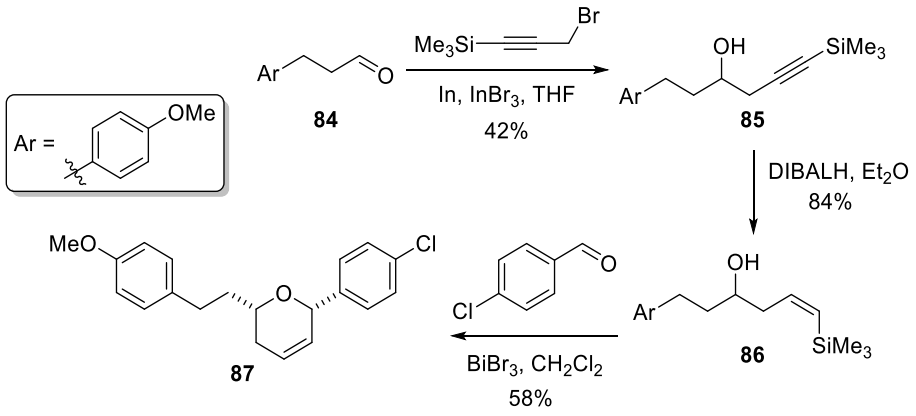
Scheme 18. Proposed biosynthetic pathway for the formation of blepharocalyxin D.[22]

1.3 Results and Discussion

1.3.1 Initial studies towards the synthesis of dimeric diarylheptanoids

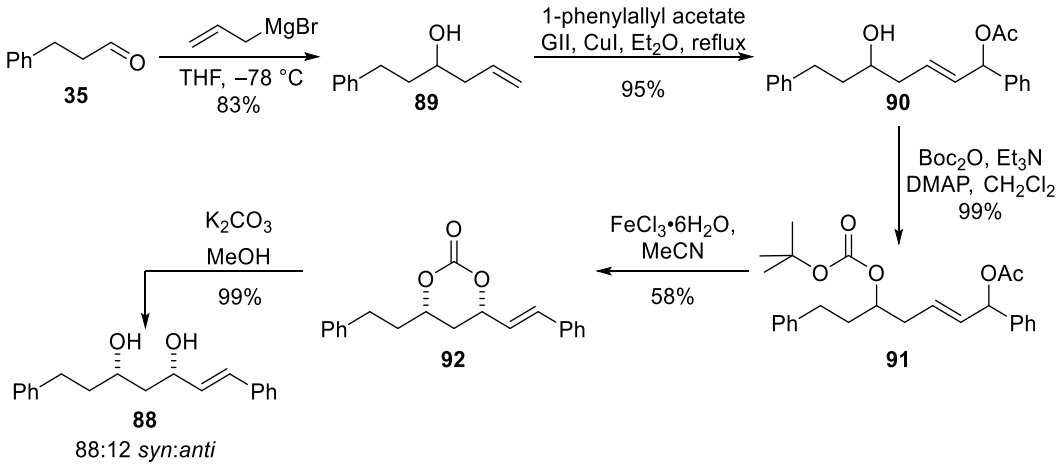
Based on this proposed biosynthetic pathway we decided to investigate the feasibility of an acid-mediated coupling between dihydropyran **16** and linear diarylheptanoid **81** to give dimeric diarylheptanoids.

Dihydropyran **87** bearing methoxy and chloro-substituted aromatic rings was selected for the initial studies. First, *Z*-homoallylic alcohol **86** was readily synthesised *via* an indium-mediated propargylation[44] and subsequent DIBALH reduction of alkyne **85** in 35% overall yield (Scheme 19). Then, a silyl-Prins cyclisation was performed by reacting homoallylic alcohol **86** with *p*-chlorobenzaldehyde in the presence of $InCl_3$ achieving a 40% yield of the desired dihydropyran **87** as a single diastereomer. The *syn* configuration was determined by ^{1}H-NMR spectroscopy and comparison with reported analogues.[15,22] Other reaction conditions were investigated for the cyclisation including the use of $BF_3{\cdot}OEt_2$ and $BiBr_3$[45] giving 34% and 58% yield of the required product, respectively.



Scheme 19. Synthesis of dihydropyran **87**

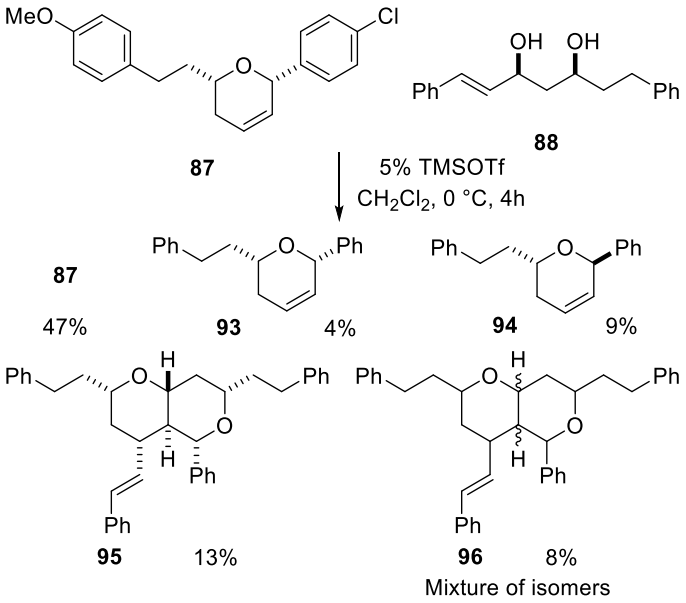
Diol **88** was prepared following the approach of Cossy *et al.*[46] Allylation of dihydrocinnamaldehyde **35** with allyl magnesium bromide gave vinyl alcohol **89** (Scheme 20). A cross-metathesis with 1-phenylallyl acetate in the presence of Grubbs II catalyst (GII) and CuI[47] produced *E*-alkene **90**, which was transformed into carbonate **91** upon treatment with Boc anhydride, DMAP and Et_3N. **91** was then treated with $FeCl_3$ to give carbonate **92** in 58% yield. $InCl_3$ was tested as an alternative Lewis acid but a poor yield of 25% was isolated. Finally, ring opening using K_2CO_3 in MeOH gave the desired diol **88** as a mixture of diastereomers, 88:12 in favour of the *syn*-diastereomer.



Scheme 20. Synthesis of diol **88**

The proposed coupling of dihydropyran **87** and diol **88** was then investigated in the presence of 5% TMSOTf in dry dichloromethane at 0 °C. The crude mixture was purified by column chromatography. Interestingly, the starting dihydropyran **87** was returned unchanged and new products were found to originate solely from diol **88**. *Syn*- and *anti*-dihydropyrans **93** and **94**

were isolated in 4% and 9% yield, dimeric diarylheptanoid **95** in 13% yield and a mixture of dimeric diarylheptanoids **96** in 8% yield.



Scheme 21. Acid-mediated reaction of dihydropyran **87** and diol **88**

The structures of the dihydropyrans were determined by NMR studies. Dihydropyran **93** had a similar ^{1}H NMR spectrum to **87** except for the aromatic region, thus its relative stereochemistry was determined as *syn*. The relative stereochemistry of *anti*-dihydropyran **94** was established by 2D NOESY where 6-H showed correlation to 5-H_{eq}, and 2-H correlated to the alkene proton 3-H (Figure 6).

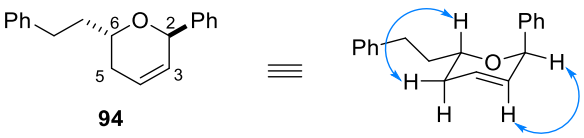


Figure 6. Diagnostic NOESY correlations of **94**

The structure and relative stereochemistry of dimeric diarylheptanoid **95** was determined by comparison of its ^{1}H and ^{13}C NMR spectra with the data of blepharocalyxin D analogue **97** which had been previously synthesised within our group and for which crystallographic data confirmed its stereochemistry.[41] Analogue **97** only differs from the isolated compound **95** by the presence of a 9-*p*-methoxyphenethyl side chain rather than the 9-phenylethyl group. The comparison of the ^{1}H and ^{13}C NMR spectra of analogues **95** and **97** (Figure 7 & Figure 8) illustrates the close correspondence present between them, confirming the structure and relative stereochemistry of the isolated bicyclic compound **95**.

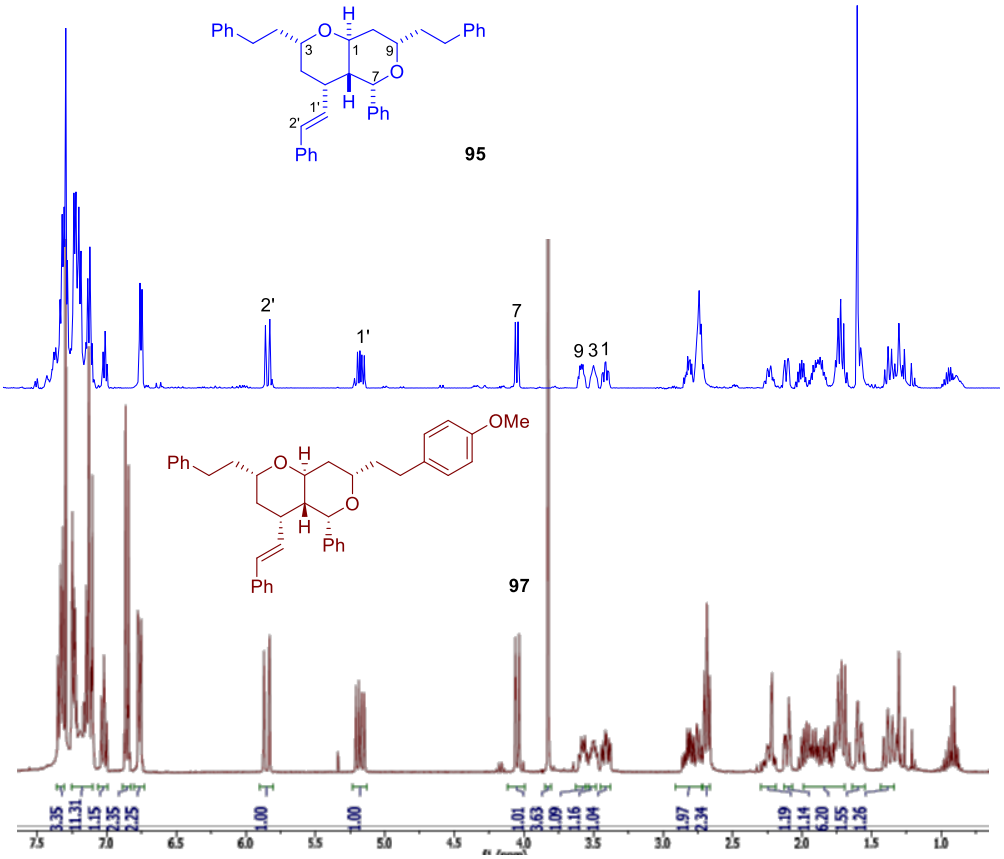


Figure 7. ^{1}H NMR spectra of analogue **97** and isolated compound **95**

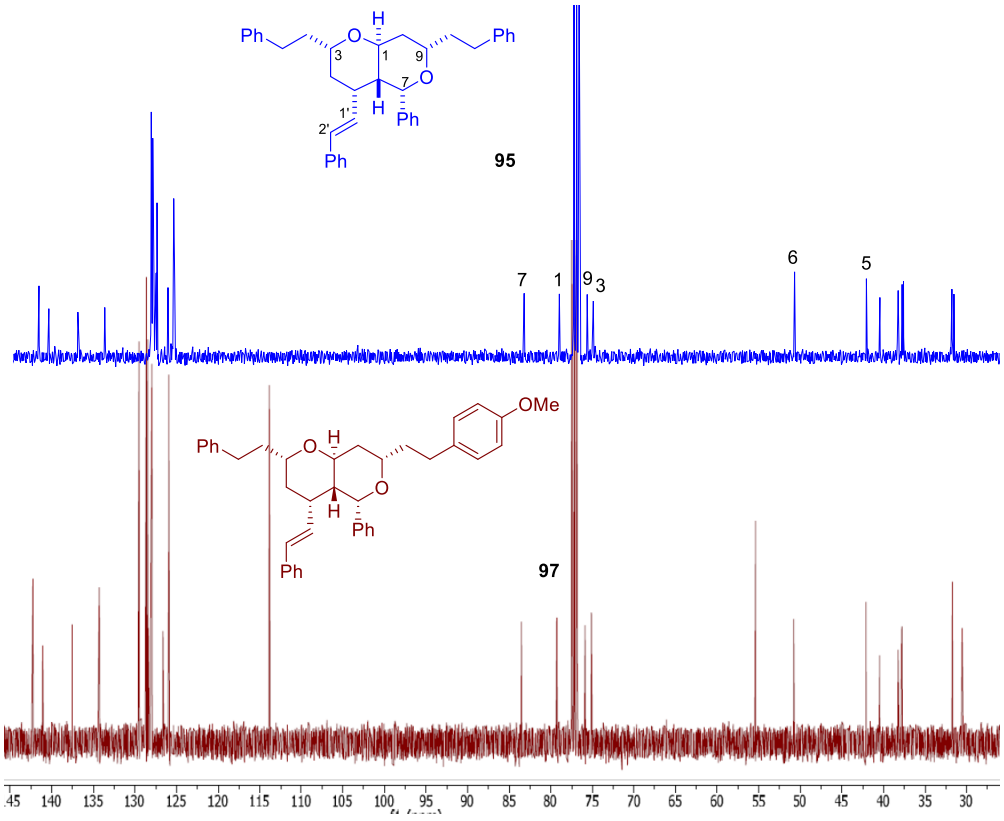
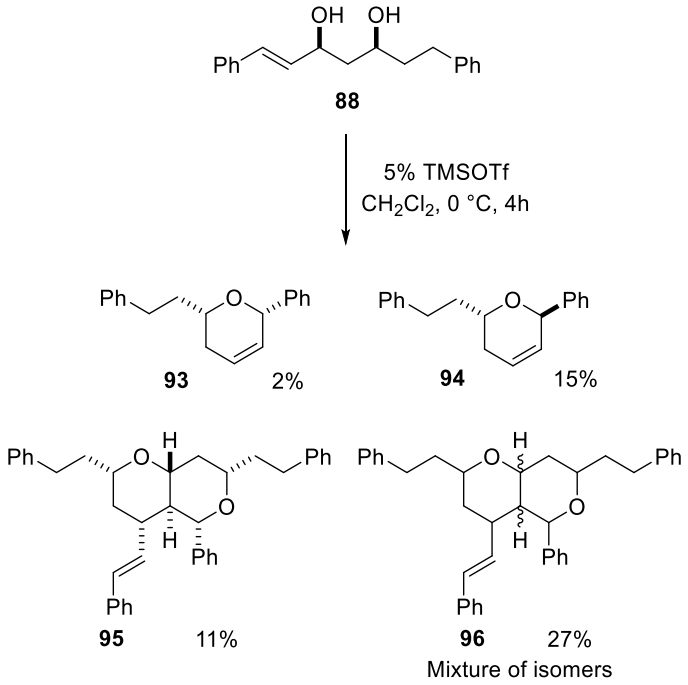


Figure 8. ^{13}C NMR spectra of analogue **97** and isolated compound **95**

This result indicated that pre-formed dihydropyran **87** was not required for the synthesis of the dimeric diarylheptanoids. To confirm this, diol **88** was treated with 5% TMSOTf in anhydrous dichloromethane at 0 °C (Scheme 22). As anticipated, after column chromatography, *syn*- **93** and *anti*-dihydropyrans **94** were isolated in 2% and 15% yield respectively, along with 11% of the corresponding blepharocalyxin D analogue **95** and 27% of a mixture of dimeric diarylheptanoid isomers **96**.

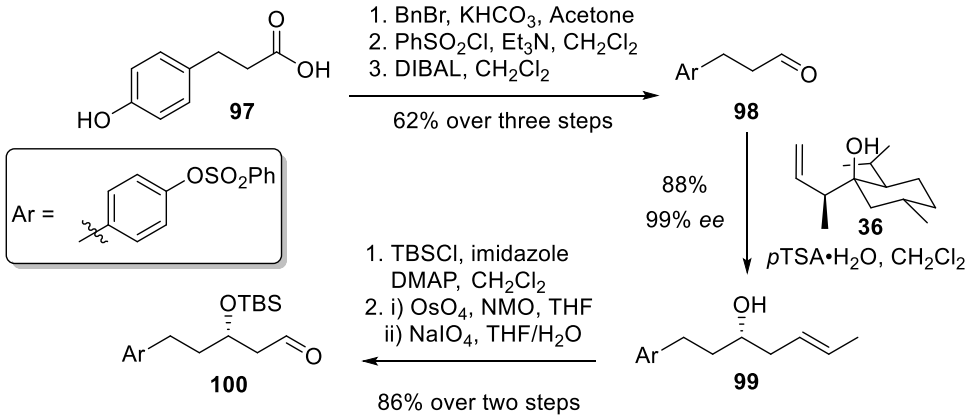


Scheme 22. Acid-mediated reaction of diol **88**

As both *anti*-**7** and *syn*-diarylheptanoids **6** have been isolated from the seeds of *A. blepharocalyx* (Figure 2),[48] our next goal was to investigate if the outcome of an acid-mediated dimerisation of each diastereomer would lead to a different outcome.

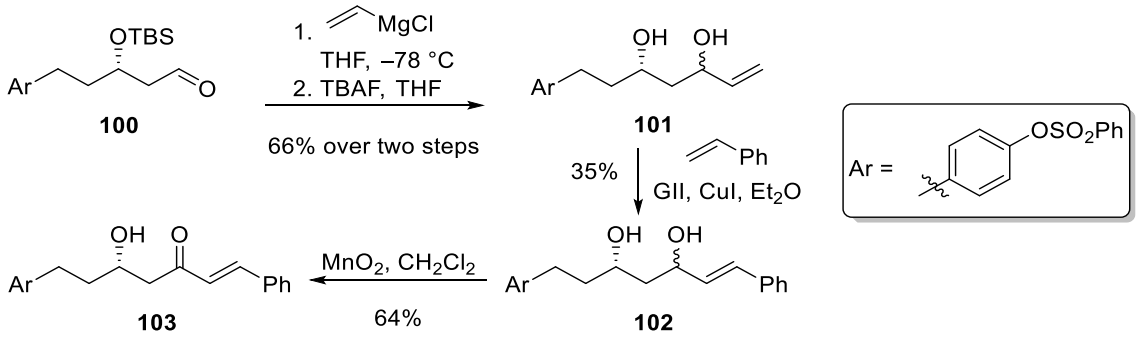
1.3.2 Enantioselective synthesis of diols 104 and 106 and their acid-mediated cyclisation

The enantioselective synthesis of the required diols **104** and **106** was undertaken using a similar approach to that previously described by Cons.[41] Aldehyde **100** was synthesised from commercially available 3-(4-hydroxyphenyl)propionic acid **97** in 5 steps and 47% overall yield. This sequence included two keys steps, a Nokami crotyl transfer reaction[30] with **98** giving alcohol **99** with 99% *ee*, as determined by chiral HPLC, and a "one pot" OsO_4/$NaIO_4$ oxidative cleavage of alkene **99** (Scheme 23).[41]



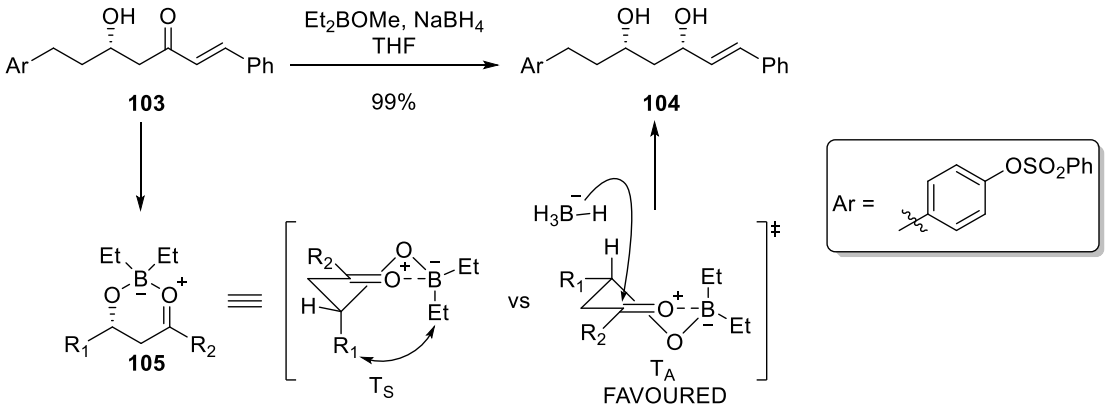
Scheme 23. Synthesis of aldehyde **100**

Reaction of aldehyde **100** with vinylmagnesium chloride and subsequent TBAF deprotection produced diol **101** as a mixture of diastereomers (Scheme 24). Cross-metathesis of **101** with styrene and Grubbs II catalyst (GII) gave alkene **102** with exclusive *E*-geometry of the double bond. As the mixture of diastereomers could not be separated by column chromatography, a selective allylic oxidation with manganese dioxide[49] was performed giving β-hydroxyketone **103**.



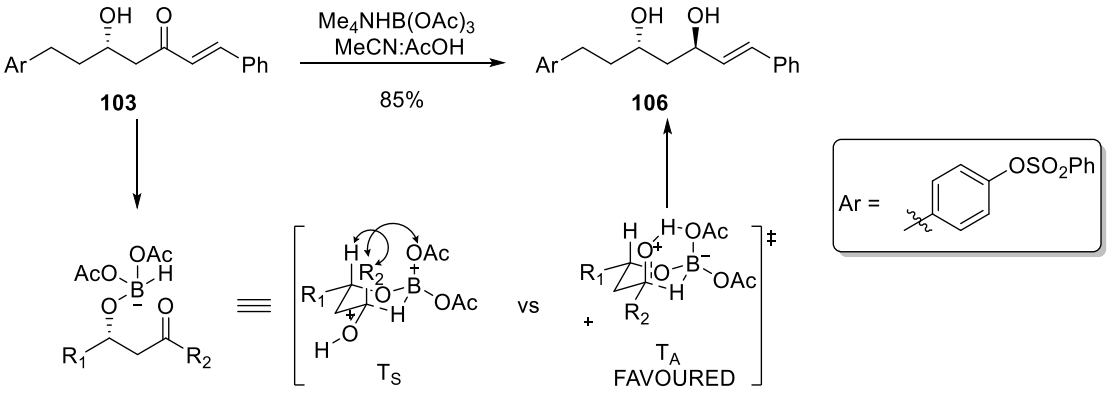
Scheme 24. Synthesis of β-hydroxyketone **103**

To complete the synthesis of the required *syn*- and *anti*-dihydroxy-diarylheptanoids directed reductions were required. *Syn*-diol **104** was obtained *via* a Narasaka-Prasad reduction[50,51] by treatment of β-hydroxyketone **103** with Et_2BOMe and $NaBH_4$ with a 99:1 *dr*, as determined by ^1H NMR spectroscopy (Scheme 25). The selectivity of the reaction is achieved by the intermolecular delivery of the hydride to **105** formed by chelation with boron. Unfavourable steric interactions of the ethyl group with R_1 destabilise T_S favouring transition state T_A resulting in the hydride attacking from the top face.[50]



Scheme 25. Narasaka-Prada asymmetric reduction of β-hydroxyketone **103** to *syn*-diol **104**

For the preparation of the *anti*-diol **106** an Evans-Saksena directed reduction[52,53] was performed. β-Hydroxyketone **103** was treated with $Me_4NHB(OAc)_3$ in a 1:1 mixture of MeCN:AcOH giving *anti*-diol **106** with a 9:1 *dr*, as determined by ^{1}H NMR spectroscopy. Evans and co-workers[52] state that the stereoselectivity of the reaction reflects a competition between chair-like transitions states T_A and T_S, each of which involves intramolecular hydride delivery. Unfavourable steric interactions between R_2 and OAc destabilise T_S favouring transition state T_A with R_2 in an equatorial position (Scheme 26).



Scheme 26. Evans-Saksena asymmetric reduction of β-hydroxyketone **103** to *anti*-diol **106**

The ^{1}H NMR spectra below show the olefinic and methine regions of *syn*-diol **104** and *anti*-diol **106** (Figure 9). It is possible to observe the presence of very small quantities of *syn*-diol present in the sample of *anti*-diol.

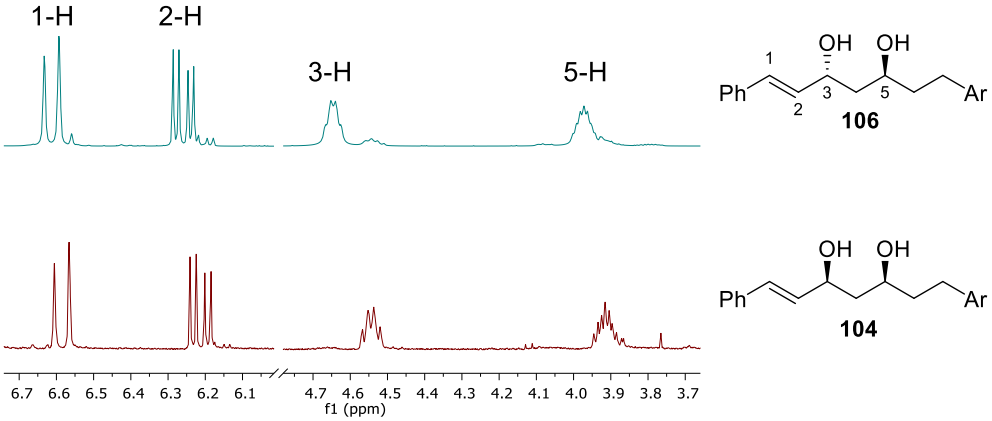


Figure 9. Diagnostic region of the ^{1}H NMR spectra of *syn*-**104** and *anti*-diol **106** ($CDCl_3$, 400 MHz)

Having synthesised diols **104** and **106**, these were treated separately with 5% TMSOTf in CH_2Cl_2 at 0 °C with stirring for 5 h. *Syn*-diol **104** gave *syn*- and *anti*-dihydropyrans **107** and **108** in 12% and 5% yield respectively along with 17% of dimeric diarylheptanoid **109**, whereas the *anti*-diol **106** produced 3% and 15% yield of **107** and **108** and 31% yield of dimeric analogue **109** (Figure 10). Hence, in further investigations only *anti*-diols were used.

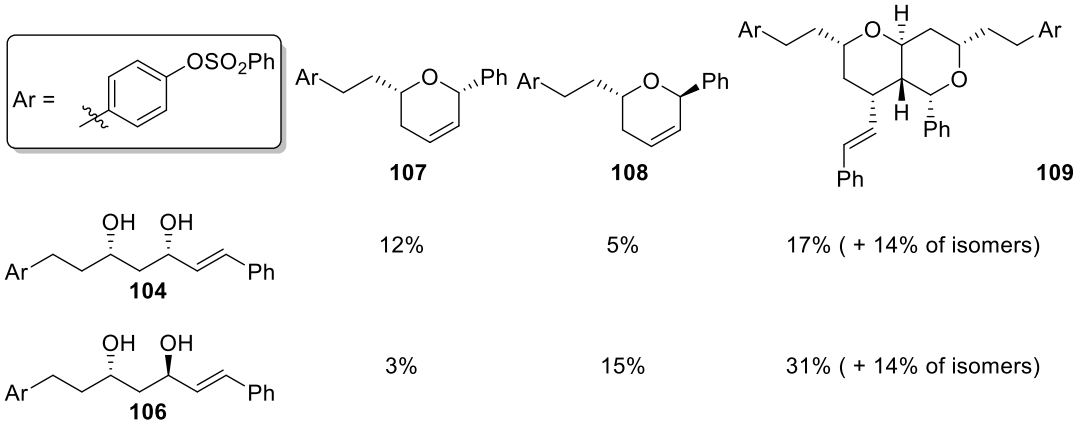
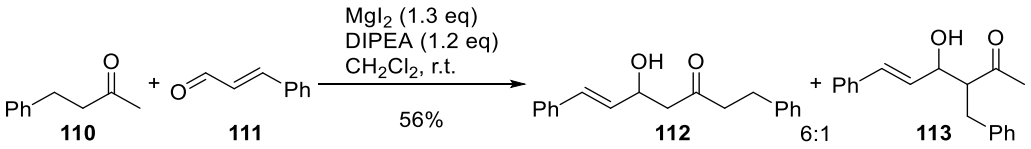


Figure 10. Isolated products from the acid-mediated cyclisations of *syn*-**104** and *anti*-diols **106**

1.3.3 Two steps synthesis of racemic diols and optimisation of the acid-mediated coupling reaction

At this point of the research our attention turned to the optimisation of conditions for the dimerisation reaction, aiming to increase the yield of the blepharocalyxin D analogue with all the side chains in equatorial positions. Ideally, a shorter synthetic approach to *anti*-diols than that shown in Scheme 20 was required. Wei and co-workers[54] reported a regioselective aldol addition of unsymmetrical ketones with aldehydes using MgI_2 as promoter. They synthesised

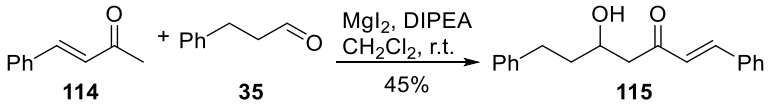
the required β-hydroxyketone **112** as an inseparable 9:1 mixture of isomers. We hoped that this mixture could be separated after reduction to the required diol. Thus, following this literature procedure, 4-phenyl-2-butanone **110**, cinnamaldehyde **111**, MgI_2 and *N,N*-diisopropylethylamine were stirred at room temperature for 2 h and after an acid work-up a 56% yield of a 6:1 mixture of regioisomers **112** and **113** was obtained (Scheme 27).



Scheme 27. Aldol reaction of aldehyde **111** and ketone **110**

In the case of unsymmetrical ketones such as **110**, deprotonation of both carbonyl α-carbons can occur, and the use of a bulky amine is intended to favour deprotonation of the more available methyl group. Unfortunately, in this case, deprotonation at the internal α-carbon of the carbonyl is not completely avoided leading to formation of **113**.

Thus, the use of enone **114** instead of ketone **110** should avoid the undesired deprotonation and only the required β-hydroxyketone **115** should be isolated. Hence, 4-phenyl-3-buten-2-one **114** and dihydrocinnamaldehyde **35** were treated with Hünig's base and MgI_2, and only β-hydroxyketone **115** was isolated in 45% yield (Scheme 28). In an attempt to improve this yield, a 50% increment on the equivalents of the base and Lewis acid were used but a lower yield (19%) of **115** was isolated. Although the inseparable mixture of regioisomers was avoided the yield was very low compared to the 81% yield reported by Wei.[54]

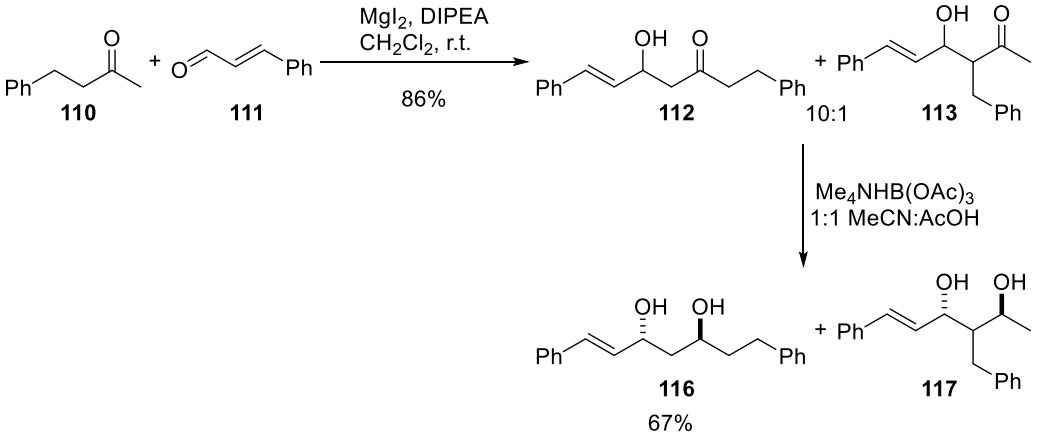


Scheme 28. Aldol addition of aldehyde **35** and enone **114**

After these disappointing results, it was decided to continue using 4-phenyl-2-butanone **110** and cinnamaldehyde **111** as starting materials and to optimise the reaction conditions (Scheme 27). Firstly, increasing the equivalents of MgI_2 (1.5 eq.) and *i*-Pr_2NEt (1.6 eq.) and a slower addition of the base resulted in a lower 36% yield but improved regioselectivity with a 10:1 ratio of isomers, suggesting that the slow addition of base improved the selectivity. In this reaction, TLC analysis of the crude reaction mixture after the acidic work-up (2N HCl) showed the presence of news spots, suggesting that the use of acid was leading to the formation of further products and

so causing a decrease in the yield of **112**. Changing to a basic work-up ($NaHCO_3$) increased the yield of **112** to 67%.

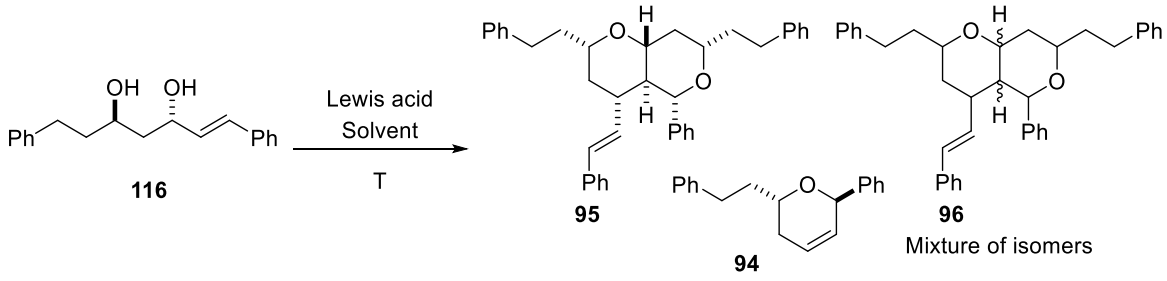
As magnesium iodide is light sensitive, the reaction was protected from light and a syringe pump was used to add the base very slowly resulting in 86% isolated yield of a 10:1 inseparable mixture of regioisomers **112** and **113** (Scheme 29). With this improved yield, β-hydroxyketone **112** was reduced using Evans-Saksena directed reduction to obtain *anti*-diol **116** in 67% yield and 5:1 *dr*. As expected, diol **117** was evident in the crude mixture by both TLC and ^{1}H NMR spectrum but was readily removed by column chromatography.



Scheme 29. Two step synthesis of *anti*-diol **116**

Although this reaction sequence was not enantioselective, it was short and simple to perform on a multigram scale producing the required substrate **116** to continue further investigations on the dimerisation reaction.

Different reaction conditions were investigated with the aim of improving the yield of blepharocalyxin D analogue **95**. First, diol **116** was treated with TMSOTf for 2 h at four different temperatures: room temperature, 0, −10 and −30 °C (Scheme 30). After standard work-up, the four crude mixtures were analysed by ^{1}H NMR spectra (Figure 11).



Scheme 30. Acid-mediated reaction of *anti*-diol **116** at different temperatures

^{1}H NMR analysis showed that the reactions at room temperature and 0 °C gave no starting material and *anti*-dihydropyran **94** and dimeric diarylheptanoid **95** were produced. The reaction at −10 °C showed a significant amount of starting diol **116** and a very small amount of *anti*-dihydropyran **94** was detected. When the reaction was performed at −30 °C mainly starting *anti*-diol **116** was observed.

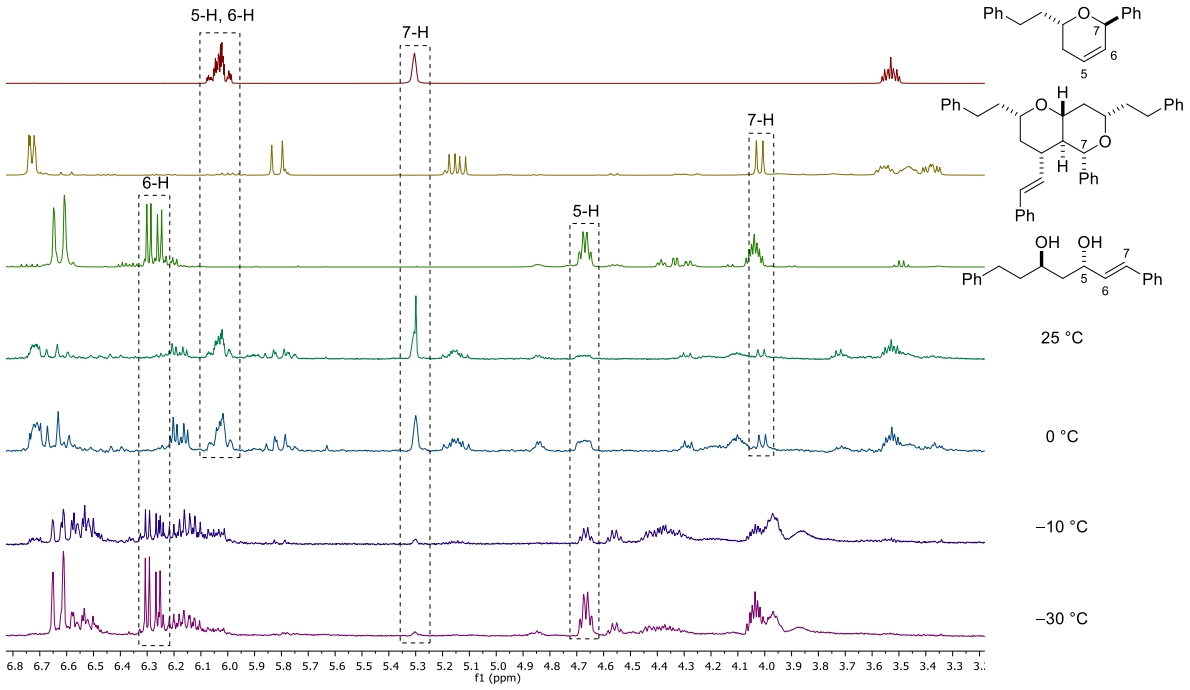


Figure 11. ^{1}H NMR spectra comparison among standard compounds **94**, **95** & **116** and crude reaction mixtures

Having set the optimal temperature at 0 °C, several non-nucleophilic Lewis acids which are commonly used for Prins cyclisations[35,55,56] were tested. Thus, *anti*-diol **116** was treated separately with 5% of seven different Lewis acids: $Yb(OTf)_3$, $Ag(OTf)_3$, $Sc(OTf)_2$, $Sn(OTf)_3$, $In(OTf)_3$, $Bi(OTf)_3$ and $BF_3{\cdot}Et_2O$, with stirring for 7 h at 0 °C. Following a standard work-up the crude mixture of each reaction was analysed by ^{1}H NMR spectroscopy. It was apparent that reactions with $Yb(OTf)_2$ and $Ag(OTf)_3$ returned starting material after 7 hours. In the case of $Sc(OTf)_3$ no starting material was apparent, but a complex mixture had been formed and no further investigation was undertaken. The reactions with $Sn(OTf)_2$, $In(OTf)_3$, $Bi(OTf)_3$ and $BF_3{\cdot}Et_2O$ gave no starting material and *anti*-dihydropyran **94** and dimeric diarylheptanoid **95** were produced. $Sn(OTf)_3$ and $BF_3{\cdot}Et_2O$ showed the most promising results, hence, larger scale reactions with

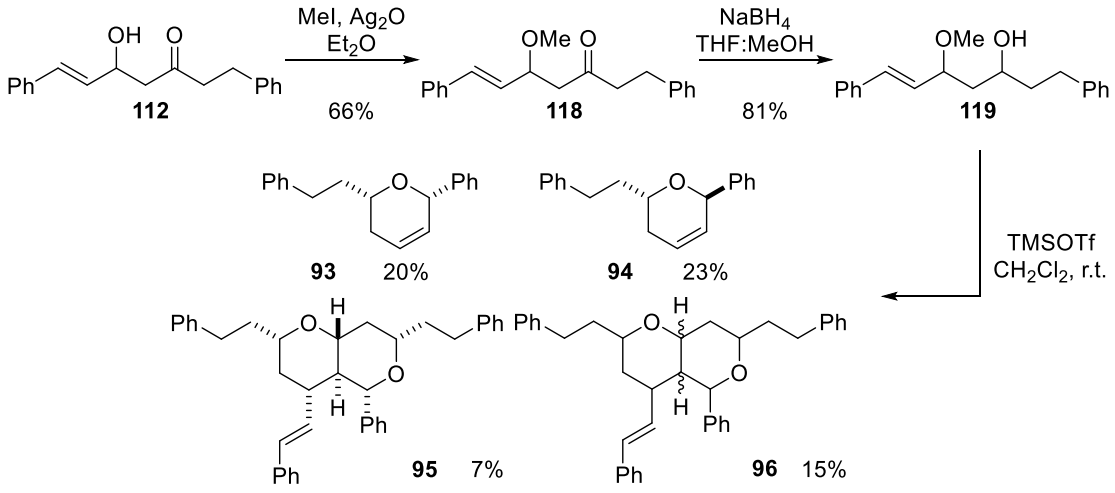
these Lewis acids were performed and after 24 h dimeric diarylheptanoid **95** was isolated in 7% and 27% yield respectively, not showing an improvement over the use of TMSOTf.

Rychnovsky and co-workers[57] have shown that non-polar solvents play an important role in reactions as Prins cyclisation favour ion-pairing, and the use of hexane has proved effective in the synthesis of bicyclic tetrahydropyrans in intramolecular Prins cyclisations.[29] Hence, hexane was tested as an alternative solvent in our dimerisation reaction, but diol **116** was not very soluble and only small quantities of products were obtained and most of the starting material was recovered.

In conclusion, none of the reaction conditions showed an improvement on the original 5% of TMSOTf in CH_2Cl_2 at 0 °C and so future studies used these conditions.

1.3.4 Synthesis and dimerisation of allylic ether 119 and acetate 121

Diarylheptanoids **6**-**9** (Figure 2) incorporating methyl and ethyl ethers were also isolated from the seeds of *A. blepharocalyx*,[11] thus we investigated if these compounds would react to give the same mixture of products under acidic conditions as the analogous diols. Hence, methyl ether **119** was synthesised in two steps and 49% overall yield from β-hydroxyketone **112**. First, **112** was methylated using iodomethane and silver(I) oxide in diethyl ether to give β-methoxy ketone **118** after three days of stirring, then subsequent reduction using $NaBH_4$ gave methyl ether **119** as a mixture of diastereomers in 81% yield.

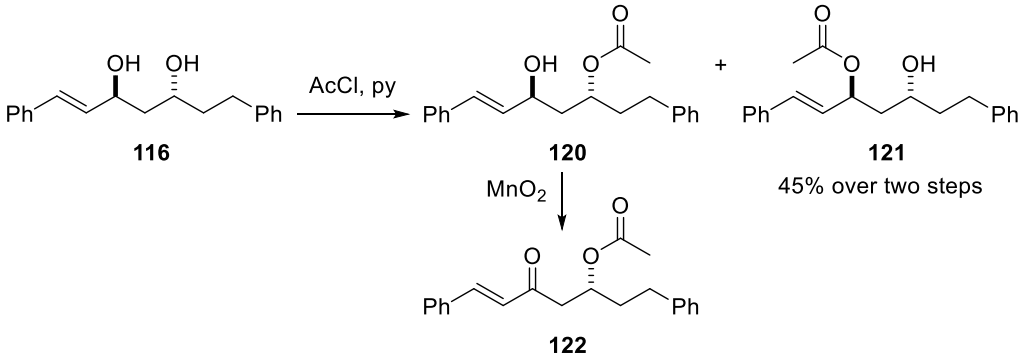


Scheme 31. Synthesis of methyl ether **119** and its acid-mediated cyclisation

Methyl ether **119** was treated with 5% TMSOTf in dichloromethane at 0 °C, however after 1 h of stirring TLC showed that no reaction had occurred. Hence the temperature was increased to

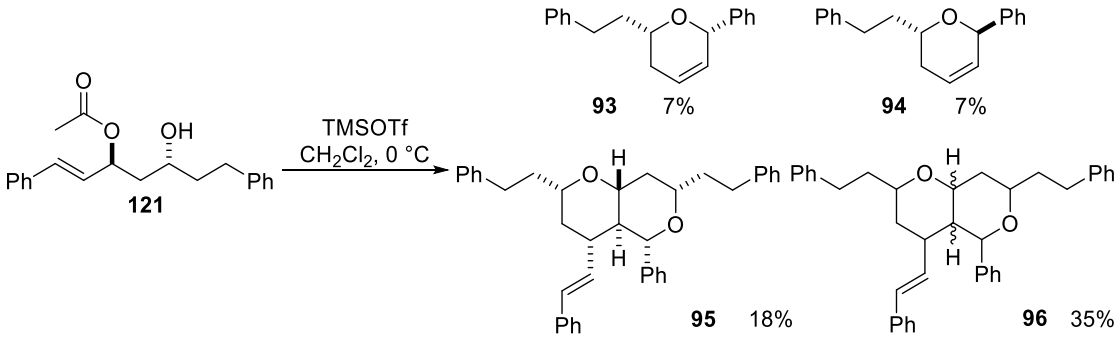
room temperature and the mixture stirred for 1 h. After purification by column chromatography *anti*-**94** and *syn*-dihydropyrans **93** were isolated in 23% and 20% yield along with blepharocalyxin analogue **95** in 7% yield and a mixture of bicyclic isomers **96** in 15% yield (Scheme 31).

Next, the effect of a better leaving group at the allylic position was investigated. Acetate **121** was synthesised in two steps from *anti*-diol **116** (Scheme 32). Standard acetylation of **116** with acetyl chloride gave an inseparable mixture of both mono-acetylated diarylheptanoids **120** and **121** in a 2.5:1 ratio favouring the required allylic acetate **121**. The mixture was treated with manganese dioxide to selectively oxidise allylic alcohol **120** to enone **122** and after purification by column chromatography, the desired ester **121** was isolated in 45% yield over the two steps.



Scheme 32. Synthesis of acetate **121**

Acetate **121** was treated with 5% TMSOTf at 0 °C for 30 minutes. After standard work-up and column chromatography *syn*- and *anti*-dihydropyrans **93** and **94** were isolated, along with 18% of dimeric diarylheptanoid **95** and 35% of a mixture of dimeric isomers **96** (Scheme 33).

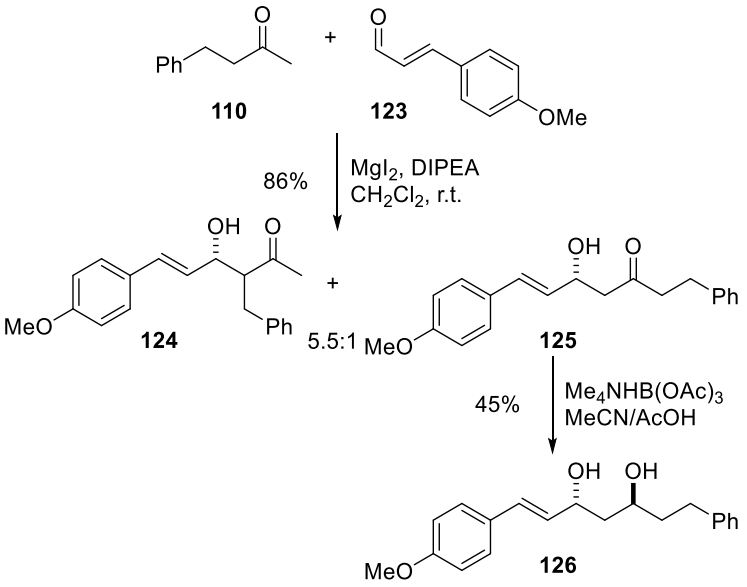


Scheme 33. Acid-mediated cyclisation of ester diarylheptanoid **121**

Hence, the presence of a good leaving group increases the rate of the reaction and favours the intermolecular reaction producing about 50% of dimeric diarylheptanoids **95** and **96** and only 14% of dihydropyrans **93** and **94**.

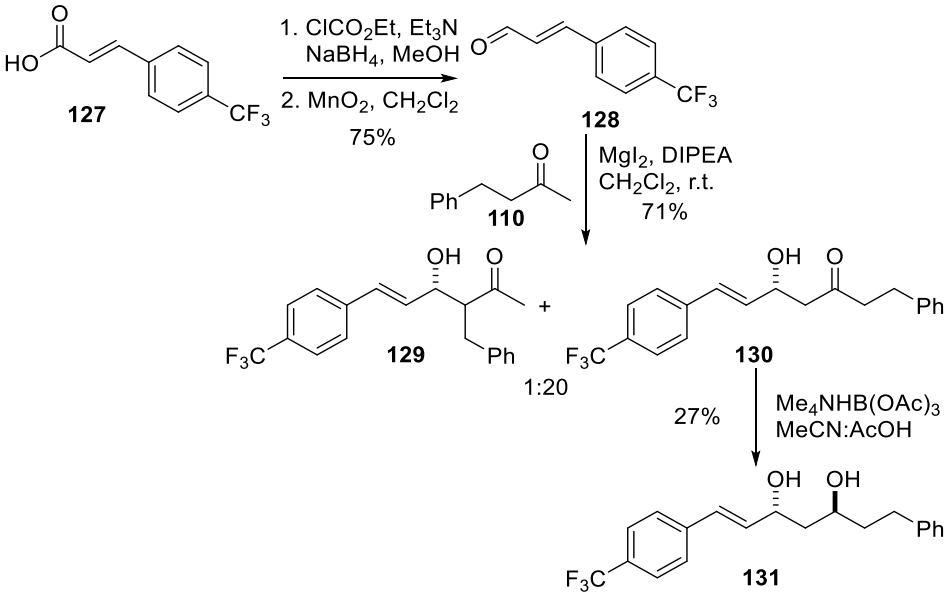
1.3.5 Effect of the electron-density on the allylic aromatic ring on the dimerisation process

Taking into consideration the results obtained so far, it was proposed that the 2,8-dioxabicyclo[4.4.0]decanes are likely to be generated *via* allylic carbocationic intermediates which could be stabilised by an electron-rich aromatic ring. To test this hypothesis two new unsaturated diols **126** and **131** with electron-rich and electron-deficient aromatic rings were synthesised *via* an aldol reaction. Treatment of commercially available *p*-methoxycinnamaldehyde **123** and 4-phenylbutan-2-one **110** with Hünig's base and MgI_2 gave an inseparable mixture of regioisomers of β-hydroxyketone **124** and **125** in 5.5:1 ratio (Scheme 34). Reduction of the mixture with $Me_4NHB(OAc)_3$ gave diol **126** containing an electron rich aromatic ring in 37% over two steps.



Scheme 34. Synthesis of dihydroxy-diarylheptanoid **126** with an electron rich aromatic ring.

For the synthesis of dihydroxy-diarylheptanoid **131** bearing an electron deficient aromatic ring, the required aldehyde **128** was not commercially available. Hence 4-(trifluoromethyl)cinnamic acid **127** was reduced with $NaBH_4$ *via* reaction of the acid with ethyl chloroformate and triethylamine giving the primary alcohol. Subsequent manganese dioxide oxidation produced the corresponding aldehyde **128** in 75% over two steps (Scheme 35). Aldehyde **128** was reacted with 4-phenylbutan-2-one **110**, MgI_2 and DIPEA giving β-hydroxyketones **129** and **130** as an inseparable mixture of regioisomers in 20:1 ratio, which after Evans-Saksena reduction, diol **131** was isolated.



Scheme 35. Synthesis of dihydroxy-diarylheptanoid **131** with an electron deficient aromatic ring.

Diols **116**, **126** and **131** were treated separately with 5% of TMSOTf at 0 °C for 1 h. Diol **131** with the electron-withdrawing *p*-trifluoromethylphenyl group simply returned starting material (Figure 12). In contrast, diol **126** containing the electron-donating methoxy group gave blepharocalyxin D analogue in 23% yield along with a further 32% of mixed dimeric products and 2% of *anti*-dihydropyran. Diol **116** containing an allylic phenyl group returned 50% of the starting material and a poor yield of cyclic products were obtained.

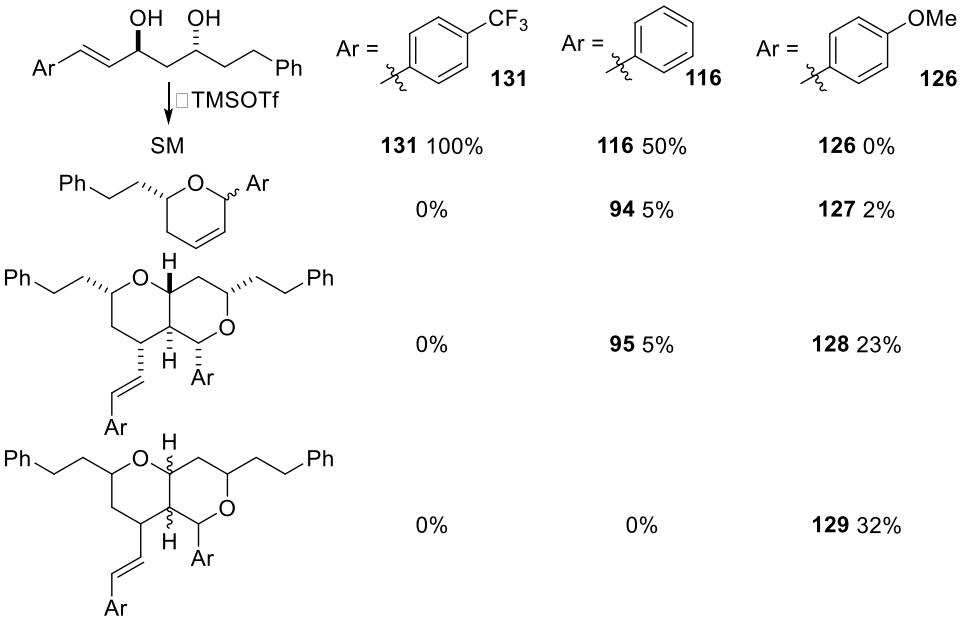


Figure 12. Acid-mediated cyclisations of dihydroxy-diols **116, 126, 131.**

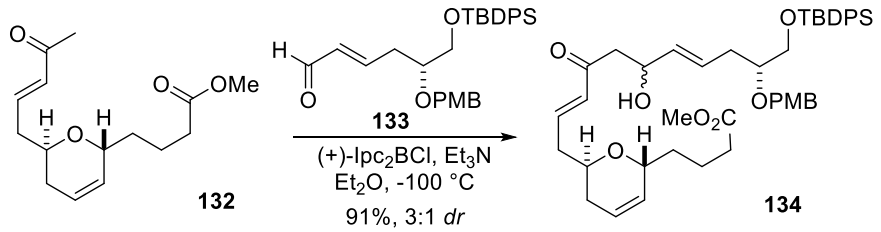
These results are in accord with the reaction proceeding *via* carbocationic intermediates stabilised by the presence of the electron-rich *p*-methoxyphenyl ring.

1.3.6 Two step enantioselective synthesis of dihydroxy-diarylheptanoids

At this point of the research, we focused our attention on the development of a short enantioselective synthesis of precursor diarylheptanoids with different aryl groups aiming to produce enantiopure dimeric diarylheptanoids.

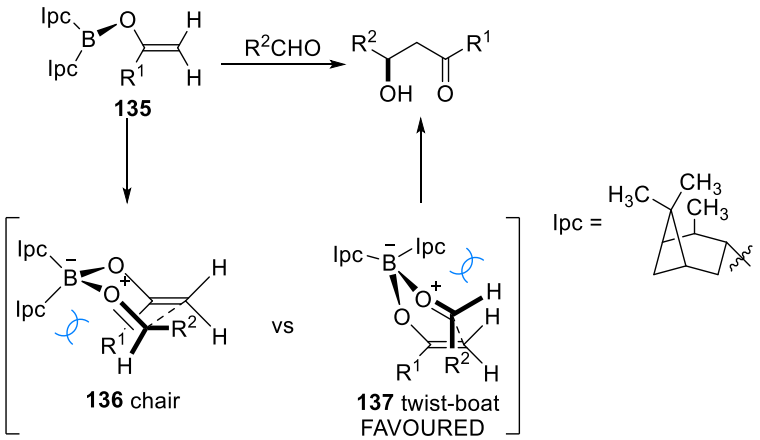
Firstly, a proline catalysed direct asymmetric aldol reaction was investigated.[58] Thus 4-phenylbutan-2-one and cinnamaldehyde were treated with L-proline in DMSO for 12 days, but unchanged starting materials were recovered. Next, a Mukaiyama aldol using (*R*)-BINOL as asymmetric catalyst and titanium tetraisopropoxide (Ti(O*i*Pr)$_4$)[59] was tested which also returned unreacted starting materials.

Paterson and co-workers have used Ipc$_2$BCl to perform several asymmetric aldol reactions with good diastereoselectivity.[60–65] For example, in the synthesis of the macrocyclic core of laulimalide, [65] reaction of **132** and **133** with (+)-Ipc$_2$BCl and Et$_3$N in Et$_2$O at −100 °C gave **134** in 91% and 3:1 *dr* (Scheme 36).



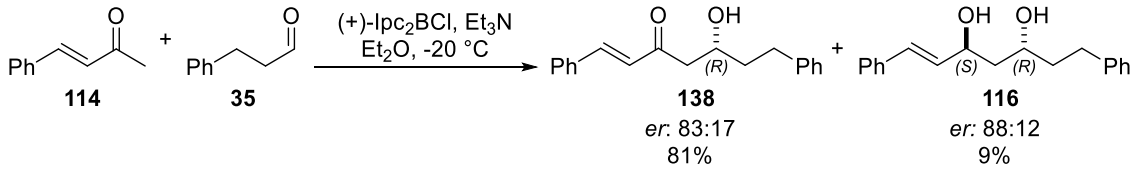
Scheme 36. Synthesis of **134** via boron aldol coupling[61]

Paterson and co-workers[66] proposed a mechanism for the reaction as illustrated in Scheme 37. The methyl ketone is converted to an enolate **135**, then reaction with aldehyde favours the twist-boat conformation **137** over the chair conformation **136** as it avoids steric interaction between R^1 and a bulky Ipc group which is apparent in the chair structure **136** (Scheme 37). This then leads to an attack of the aldehyde on the top face of the enolate **137**, which prefers to have the Ipc group tilted up out of the plane.



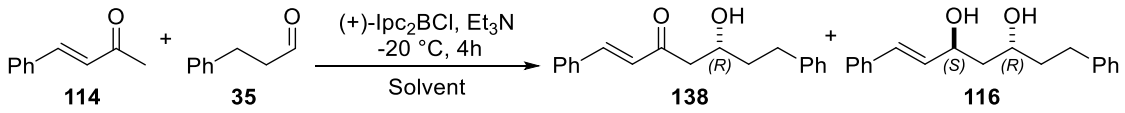
Scheme 37. Mechanism of $(Ipc)_2BCl$ aldol reaction[66]

Thus, following Paterson's conditions enone **114** and aldehyde **35** were reacted with (+)-Ipc_2BCl and Et_3N producing β-hydroxyketone **138** in 81% yield with 83:17 *er* along with a 9% of *anti*-diol **139** in 88:12 *er* as determined by chiral HPLC (Scheme 38).



Scheme 38. Synthesis of β-hydroxyketone **138** and diol **116**

In an attempt to improve the enantioselectivity of the reaction different solvents were tested. Thus, five reactions were performed under the same reaction conditions of stirring at −20 °C for 4 h using either THF, hexane, dichloromethane or toluene as the solvent. The yields and enantiomeric ratios are shown in Table 3.

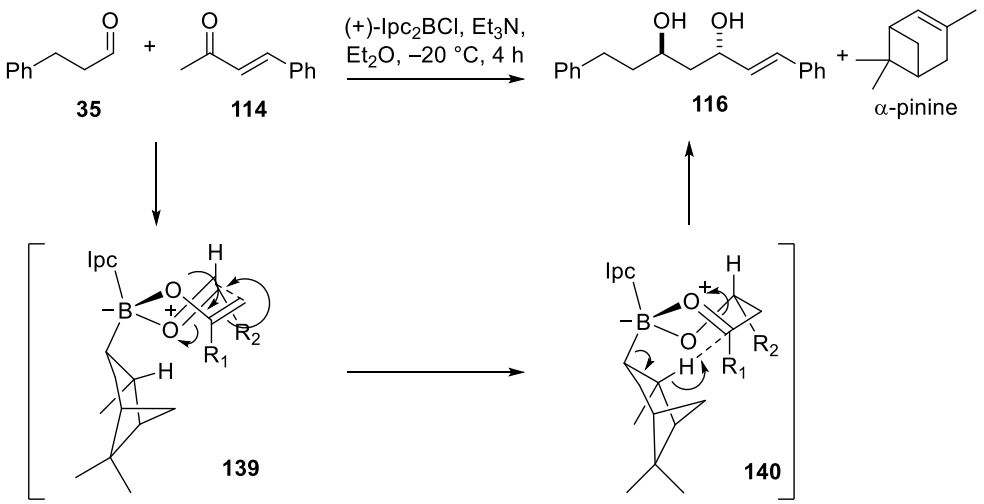


Solvent	% yield		*er*		Total yield
	138	**116**	**138**	**116**	
THF	73	6	73:27	92:8	79
Hexane	81	18	79:21	84:16	99
DCM	85	13	68:32	93:7	98
Toluene	75	14	74:26	87:13	89
Et_2O	81	9	83:17	88:12	89

Table 3. Optimisation of the $(Ipc)_2BCl$ aldol reaction

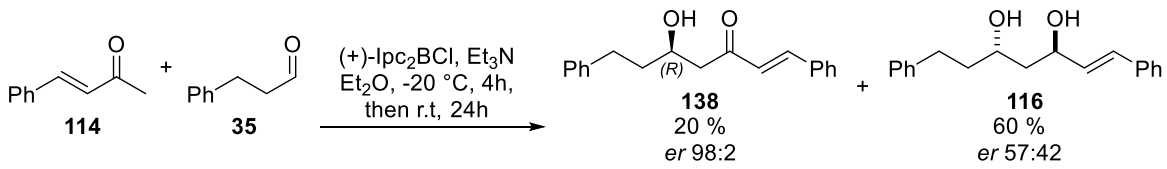
The five reactions produced good yields (>70%) of β-hydroxyketone **138**, with dichloromethane being the most efficient with 85% yield, unfortunately the use of this solvent reduce the selectivity of the reaction (68:32 *er*). THF, hexane and toluene showed better enantioselectivity (>70:30 *er*) but none of the solvent tested improved the 83:17 *er* obtained when using diethyl ether. Along with β-hydroxyketone **138**, low yields of diol **116** with different enantiomeric ratios and >98 *dr* in favour of the *anti*-diol, as determined by ^{1}H NMR spectroscopy, were also isolated. It is apparent that after the aldol reaction, reduction of hydroxyketone **138** occurred.

The mechanism of this reduction is shown in Scheme 39. Firstly, an aldol reaction between enone **114** and aldehyde **35** occurred in the twist conformation **139**, which leaves the Ipc group close enough to deliver a hydride from the bottom face of the carbonyl on **140** producing diol **116** and the loss of pinene.



Scheme 39. Mechanism of reduction with (+)-Ipc_2BCl

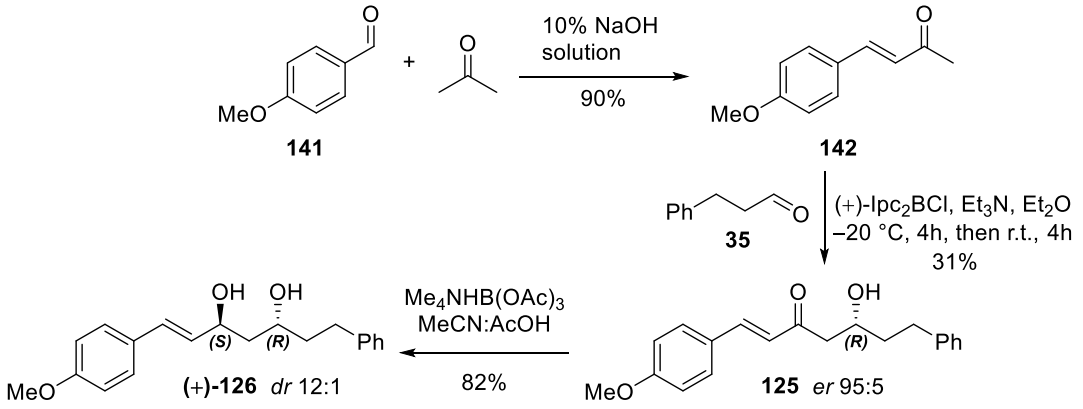
Hence, in order to improve the overall *er* of hydroxyketone **138**, enone **114** and aldehyde **35** were treated with (+)-Ipc_2BCl and Et_3N at −20 °C for 4 h to allow the aldol reaction to reach completion, then the reaction was warmed to room temperature and stirred overnight (Scheme 40). After work-up and column chromatography 20% of β-hydroxyketone **138** with 98:2 *er* was isolated along with 60% of diol **116** with 57:42 *er* as determined by chiral HPLC. In this case, the *er* of the isolated β-hydroxyketone **138** was excellent although the isolated yield (20%) was disappointing. Thus, for future reactions a continuous monitoring using chiral HPLC was performed to obtain a good selectivity without sacrificing too much yield of β-hydroxyketone **138**.



Scheme 40. Synthesis of β-hydroxyketone **138** and diol **116**

1.3.7 Synthesis of *anti*-diols (+)-126 and 126 and their acid-mediated cyclisation

Having an enantioselective route for the synthesis of hydroxyketones in hand, we pursued the synthesis of (+)-*anti*-diol **126**, with the electron-rich aromatic ring. Enone coupling partner **142** was synthesised in 90% yield from reaction of *p*-anisaldehyde **141** with acetone in the presence of a 10% solution of NaOH (Scheme 41).[67] Aldol reaction of enone **142** with aldehyde **35** using (+)-Ipc_2BCl and Et_3N produced β-hydroxyketone **125** in 31% yield and 95:5 *er*, as determined by HPLC (Figure 13). Directed reduction using $Me_4NHB(OAc)_3$ gave diol **(+)-126** in 82% yield with a *dr* of 12:1.



Scheme 41. Synthesis of (+)-*anti*-diol **126**

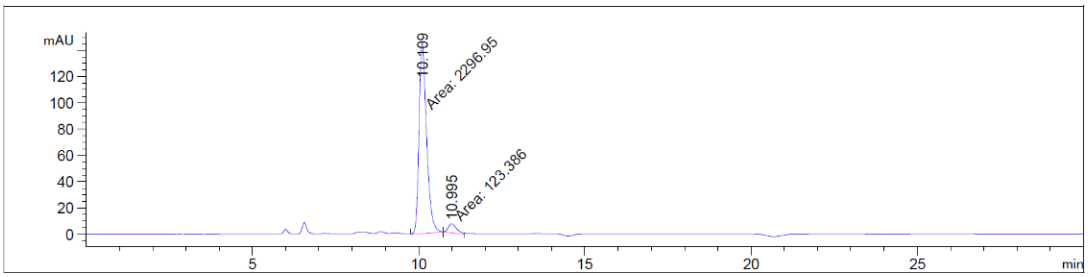
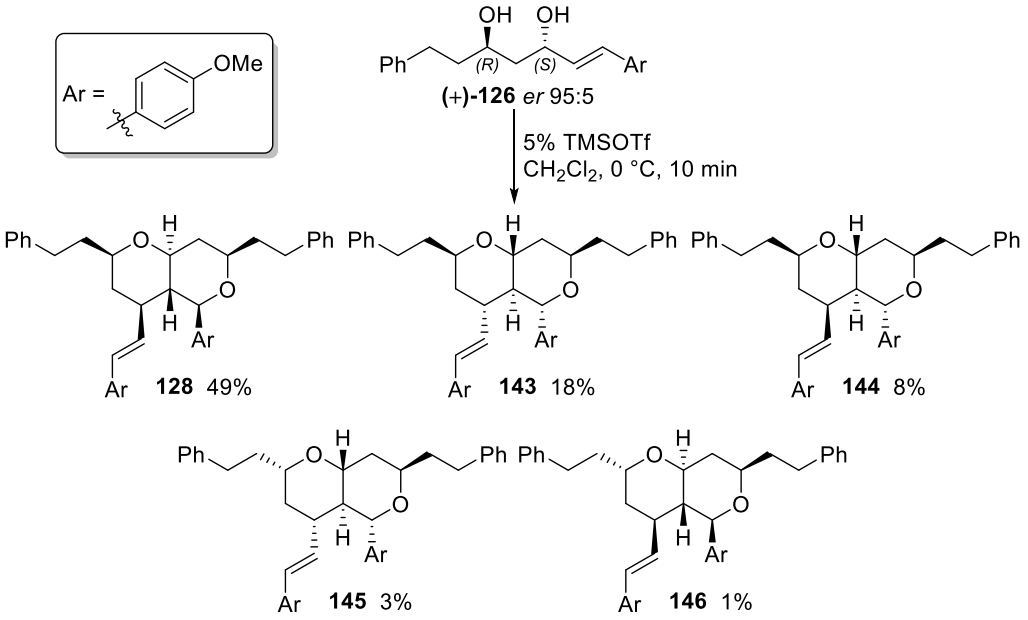


Figure 13. Chiral HPLC trace of enantioenriched hydroxyketone **125**

(+)-*Anti*-diol **126** was treated with 5% TMSOTf at 0 °C for 10 minutes. After standard work-up normal phase HPLC purification of the crude extract was performed and five dimeric compounds **128**, **143**-**146** were isolated (Scheme 42).



Scheme 42. Acid mediated cyclisation of (+)-*anti*-diol **126** (yield determined by HPLC)

The structure and relative stereochemistry of the most abundant dimeric diarylheptanoid **128** isolated was determined by comparison of its ^{1}H and ^{13}C NMR spectra with the data of analogue **95**, which had been synthesised earlier in this research project (Scheme 21). Analogue **95** differs from the isolated compound **128** by the presence two *p*-methoxyphenyl groups in the side chains at C-5 and C-7. Comparison of the ^{1}H and ^{13}C NMR spectra of analogues **95** and **128** (Figure 14 & Figure 15) illustrates the close correspondence present between them, confirming that bicyclic compound **128** has a *trans*-2,8-dioxabicyclo[4.4.0]decane framework with the four side chains in equatorial positions.

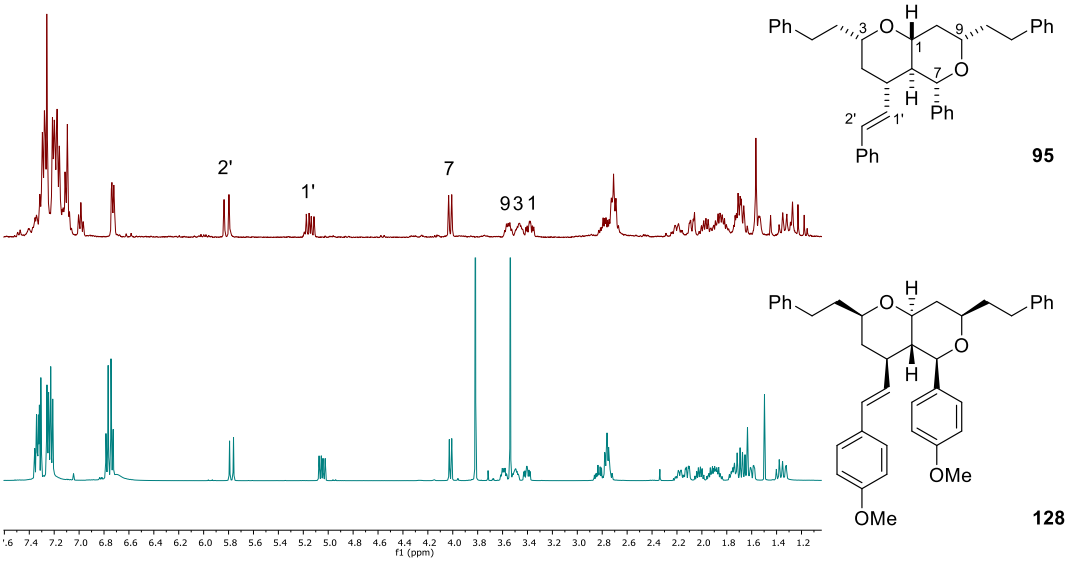


Figure 14. ^{1}H NMR spectra of analogue **95** and isolated compound **128**

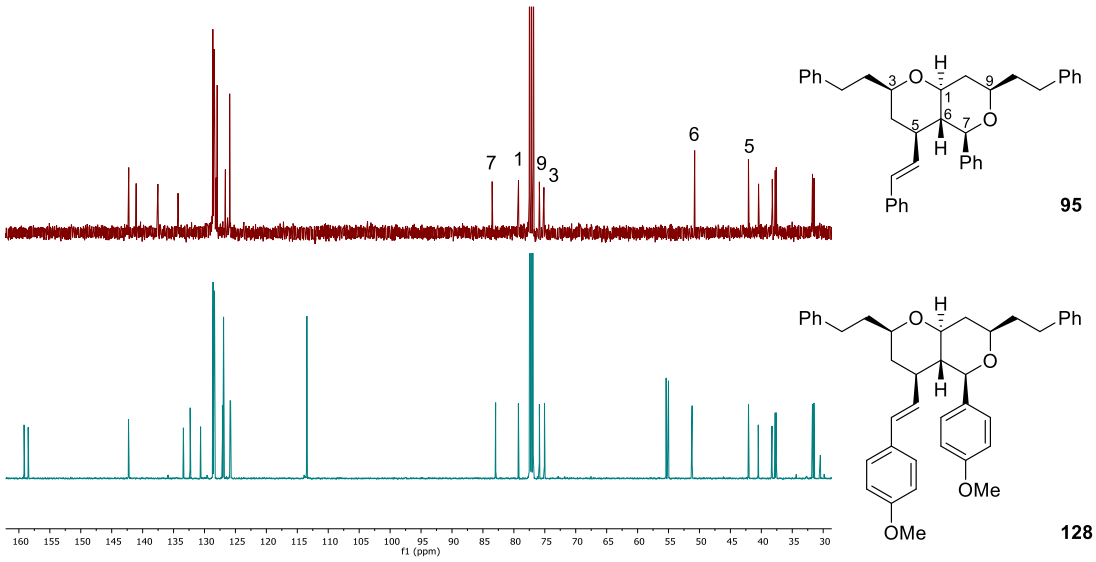


Figure 15. ^{13}C NMR spectra of analogue **95** and isolated compound **128**

The other four isolated compounds **143**-**146** have the same molecular formula ($C_{40}H_{44}O_4$) as determined by HRMS. The similarity of their ^{1}H and ^{13}C NMR spectra compared with those of blepharocalyxin D analogue **128** indicated that they are diastereomers. Extensive spectroscopic studies were used to fully assign all of the NMR spectra and the relative configuration of the side chains were determined by analysis of the coupling constants and nOe correlations. The couplings of 1-H to 6-H (*J* 10-11 Hz) and nOe correlations showed that all four products were assembled on a *trans*-2,8-dioxabicylodecane framework with the 7-methoxyphenyl ring equatorial (coupling 6-H to 7-H *J* 10-11 Hz). The structures **143-146** varied by having one or more axial side chains.

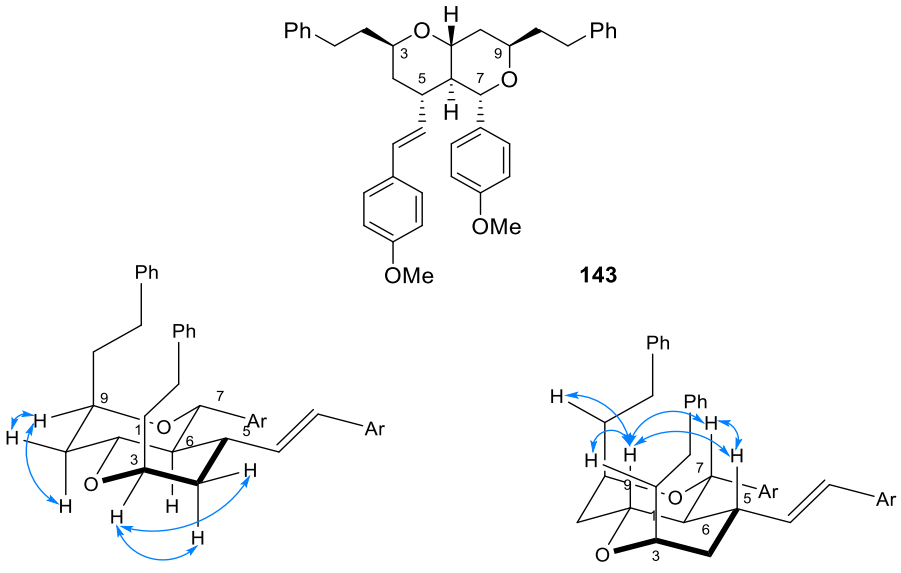
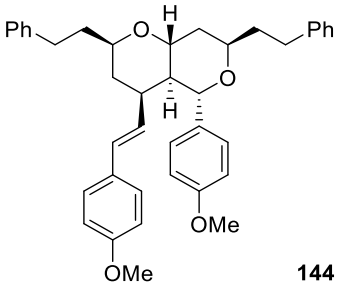


Figure 16. nOe correlations (blue) of analogue **143**

In compound **143**, 5-H shows *trans*-diaxial couplings (*J* 10 Hz) to 4-H_{ax} and 6-H indicating that the C-5 side chain is equatorial. This assignment was supported by nOe correlations among 1-H, 5-H and 7-H revealing their co-axial relationship (Figure 16). The side chains at C-9 and C-3 are axial with coupling (*J* 5-6 Hz) of the equatorial 9-H with 10-H_{ax} and equatorial 3-H with 4-H_{ax}. The small coupling (*J* 1 Hz) of 3-H with 4-H_{eq} suggest that the chair conformation is slightly flattened, due to repulsion of the side chains, bringing 3-H to almost a 90° angle with 4-H_{eq}. There were further nOe correlations of the axial 7-H to 9-CH_2 and from 1-H to both 3-CH_2 and 9-CH_2 in accord with both the C-3 and C-9 chains being axial. It is interesting to note the downfield shift of the signal assigned to 9-H from the blepharocalyxin D analogue **128** (9-H_{ax} δ 3.5) to δ 4.2 for this isomer in which 9-H is now equatorial. This proved characteristic in analysis of the data for the other isomers (Figure 18).



144

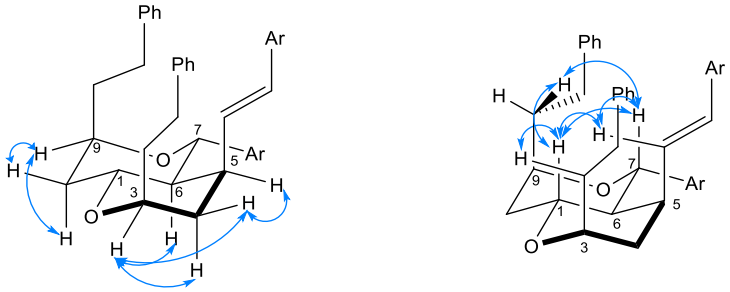


Figure 17. nOe correlations (blue) of analogue **144**

For compound **144** only the side chain at C-7 is equatorial and those at C-3, C-5 and C-9 are all axial. This was determined from the magnitude of the vicinal coupling constants (*J* 3-6 Hz) of 3-H, 5-H and 6-H and was supported by nOe correlations shown in Figure 17. There were correlations between 1-H and 3-CH_2, 5-CH, 7-H and 9-CH_2 as well as from 7-H to 5-CH and 9-CH_2. It is particularly interesting to note the downfield shift of the olefinic signals in **144** (δ 6.33 & δ 6.02) compared with the other isomers (δ 5.74 & δ 5.01) as the double bond is no longer on the same face as the aromatic ring at C-7 and hence not within its shielding region (Figure 18). In addition, there was the characteristic downfield shift of the signal assigned to 9-H to δ 4.2 for this isomer compared with blepharocalyxin D analogue **128** (9-H_{ax} δ 3.5).

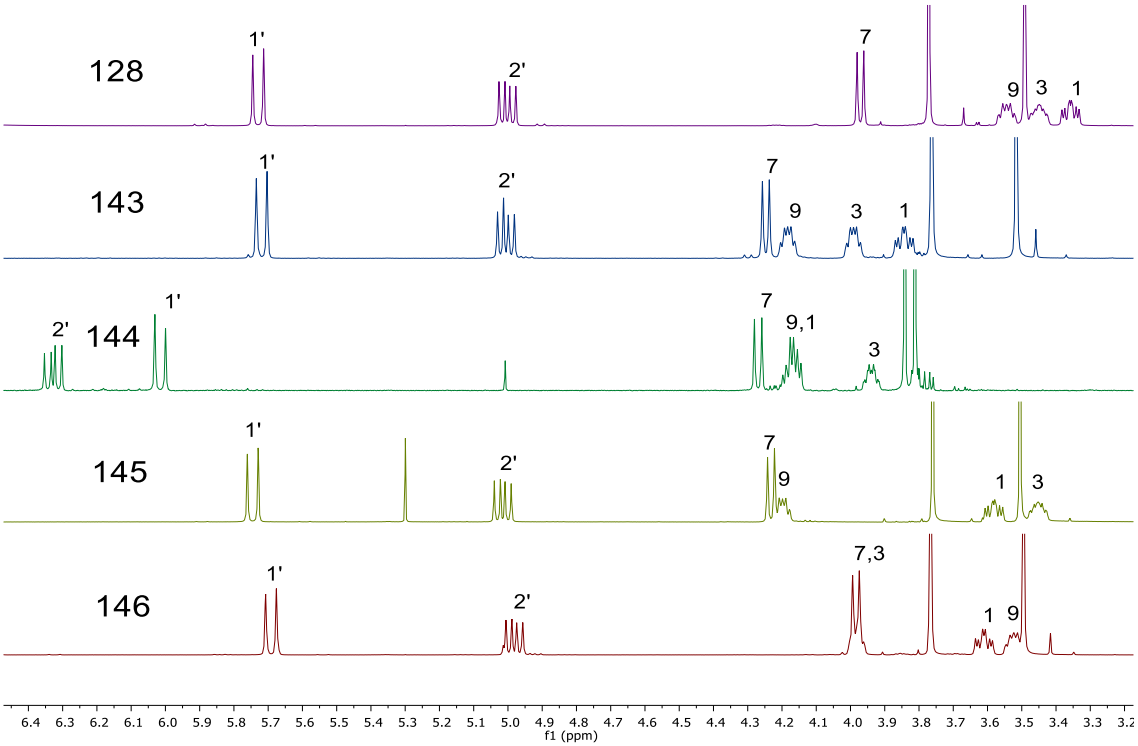


Figure 18. ^{1}H-NMR spectra of compounds **128**, **143**-**146** showing the signals of the double bond protons (1'H-2'H) and those bonded to oxygen (1-H, 3-H, 7-H & 9-H)

These left structures of the diastereomers **145** and **146** remaining to be assigned. These were isolated in small quantities (1-2 mg) but sufficient material was available for full NMR analysis.

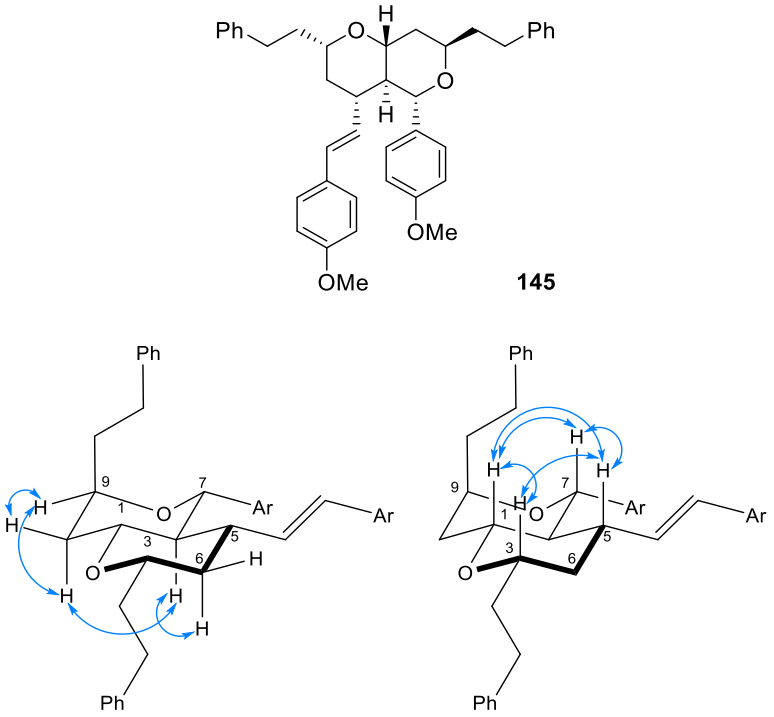
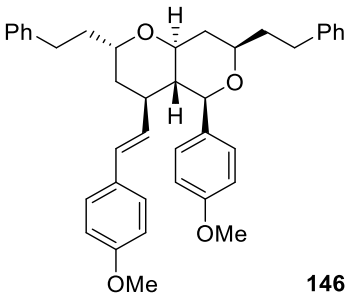


Figure 19. nOe correlations (blue) of analogue **145**

In the case of isomer **145**, only the side chain at C-9 was axial and 3-H, 5-H and 7-H all showed characteristic vicinal *trans*-diaxial couplings (*J* 10-12 Hz) in accord with the substituents at C-3, C-5 and C-7 being equatorial. This was confirmed by nOe correlations among 1-H, 3-H, 5-H and 7-H which revealed their co-axial relationship. Additionally, nOe correlations of 6-H with 4-H_{ax} and 10-H_{ax} affirmed their co-axial relationship. The assignment of the axial configuration of the side chain at C-9 was in accord with vicinal coupling (*ca*. 5 Hz) of 9-H_{eq} with 10-H_{eq} and 10-H_{ax} and nOe correlations of 9-H with both protons on C-10.



146

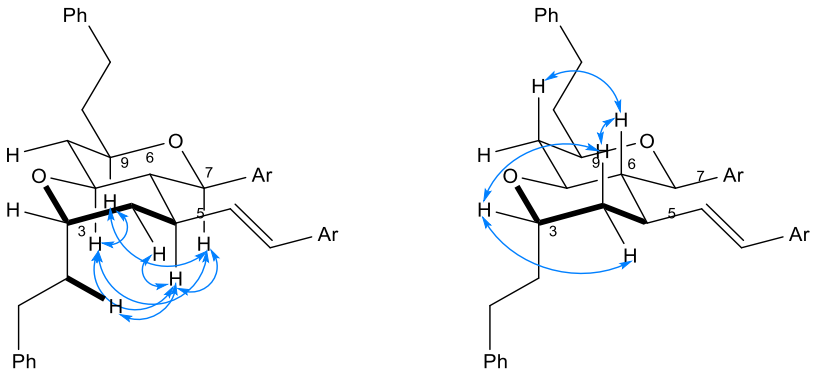
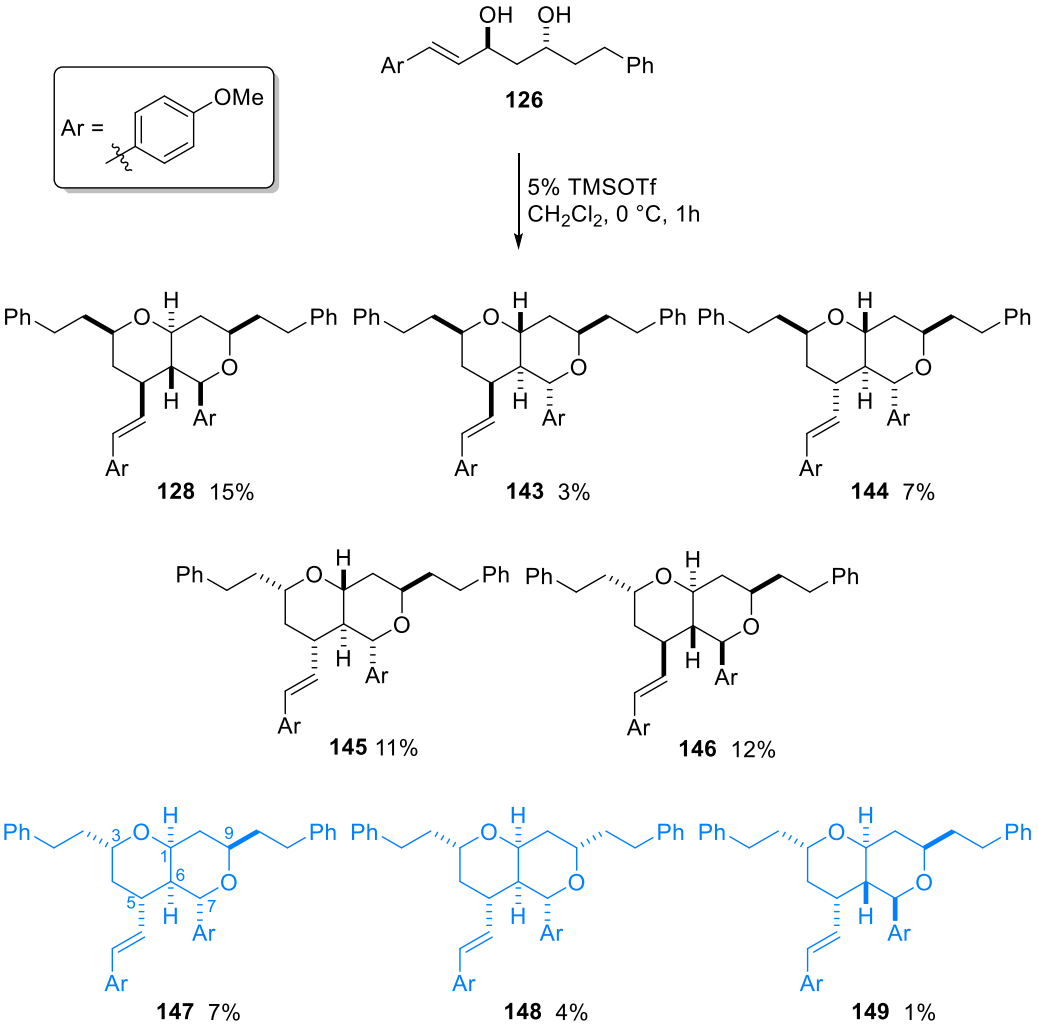


Figure 20. nOe correlations (blue) of analogue **146**

The final diastereomer was compound **146** with equatorial side chains at C-5, C-7 and C-9 with the expected vicinal *trans*-diaxial couplings (*J* 10 Hz) apparent for 5-H, 7-H and 9-H and the characteristic upfield shift of the signal assigned to 9-H_{ax} (δ 3.5). This conclusion was supported by nOe correlations among 9-H, 1-H, 5-H and 7-H revealing their co-axial relationship. The side chain at C-3 was axial and assigned from the characteristic vicinal coupling constants (*J* 2-4 Hz) and 3-H showed nOe correlations only with 4-H_2.

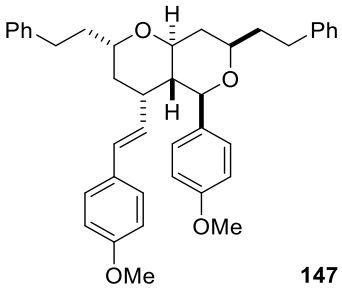
The major products **128**, **143** and **144** each arise from coupling two molecules of the major enantiomer (3*S*, 5*R*) of starting diol **126**. In contrast, the remaining two products **145** and **146** were isolated in very low yields, 3% and 1% respectively, and originate from coupling the enantiomers of the starting material. Since these two isomers have been characterised, we next

investigated if the acid-mediated cyclisation of racemic *anti*-diol **126** would produce further dimeric compounds. Thus, *anti*-diol **126** was treated with 5% TMSOTf at 0 °C and HPLC purification of the crude extract was performed (Scheme 43).



Scheme 43. Diastereomers isolated from the acid-mediated cyclisation of racemic diol **126**

Eight compounds were isolated, compounds **128**, **143**-**146** have been previously characterised from the acid-mediated reaction of (+)-*anti*-diol **126**. The three new dimeric compounds **147**-**149** have the same molecular formula $C_{40}H_{44}O_4$ as compounds **143**-**146**, as determined by HRMS. The similarity of their ^{1}H and ^{13}C NMR spectra compared with **143**-**146** indicated that they are also diastereomers. Extensive spectroscopic studies were used to fully assign the structures and the relative configuration of the side chains was determined by analysis of the coupling constants and nOe correlations.



147

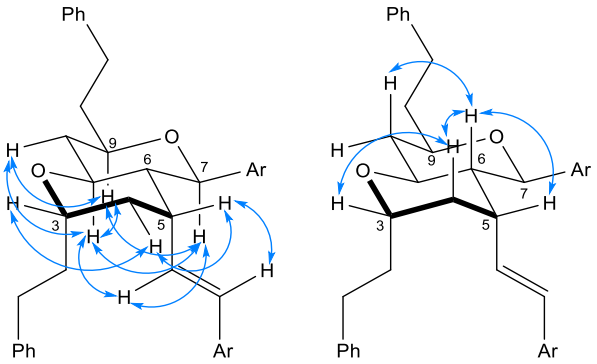
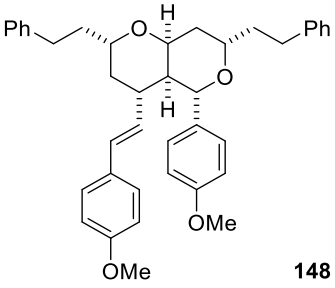


Figure 21. nOe correlations (blue) of analogue **147**

Similarly to diastereomers **143**-**146**, from nOe and the coupling of 1-H to 6-H (*J* 11 Hz) it was evident that compound **147** was assembled on a *trans*-2,8-dioxabicyclodecane framework with equatorial substituents at C-7 and C-9 (vicinal axial-axial couplings *J* 10-11 Hz) and axial side chains at C-3 and C-5 (vicinal couplings *J* 2-6 Hz). This assignment was verified by nOe studies (Figure 21) with diagnostic correlations between the axial 1-H, 5-H and 7-H whilst 3-H showed correlations only to 4-H_2.



148

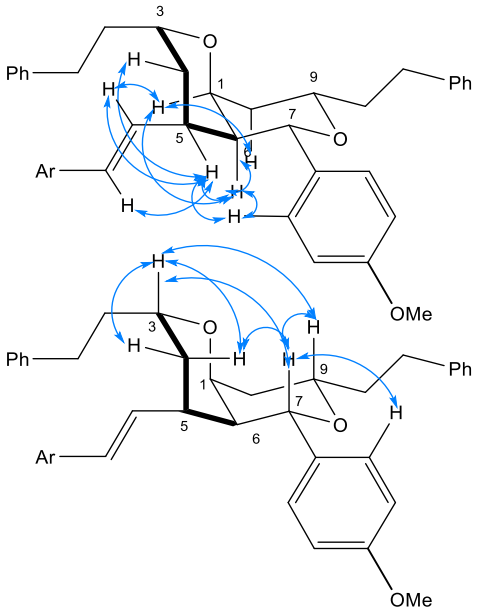


Figure 22. nOe correlations (blue) of analogue **148**

Unlike the other dimeric diarylheptanoids isolated from the acid-mediated reaction of diol **(+)-126**, compound **148** is assembled on a *cis*-2,8-dioxabicyclodecane framework as determined from the coupling constant (*J* 3Hz) of 1-H and 6-H along with their nOe correlations. The rings adopt a chair-chair conformation with equatorial side chains at C-7 and C-9 (Figure 22). The axial 7-H and 9-H show nOe correlations to each other as well as to 4-H_{ax}. The axial side chains at C-3 and C-5 were assigned by the vicinal couplings (*J* 3-5 Hz) of 3-H_{eq} and 5-H_{eq} and nOe correlations among 3-H, 10-H_{eq}, 7-H and 9-H reveal their proximity in the cis configuration of the rings. Additionally, there were nOe correlations between the aromatic protons of the 7-phenyl group and 5-H, 6-H and 7-H as well as between 1-H and 5-CH.

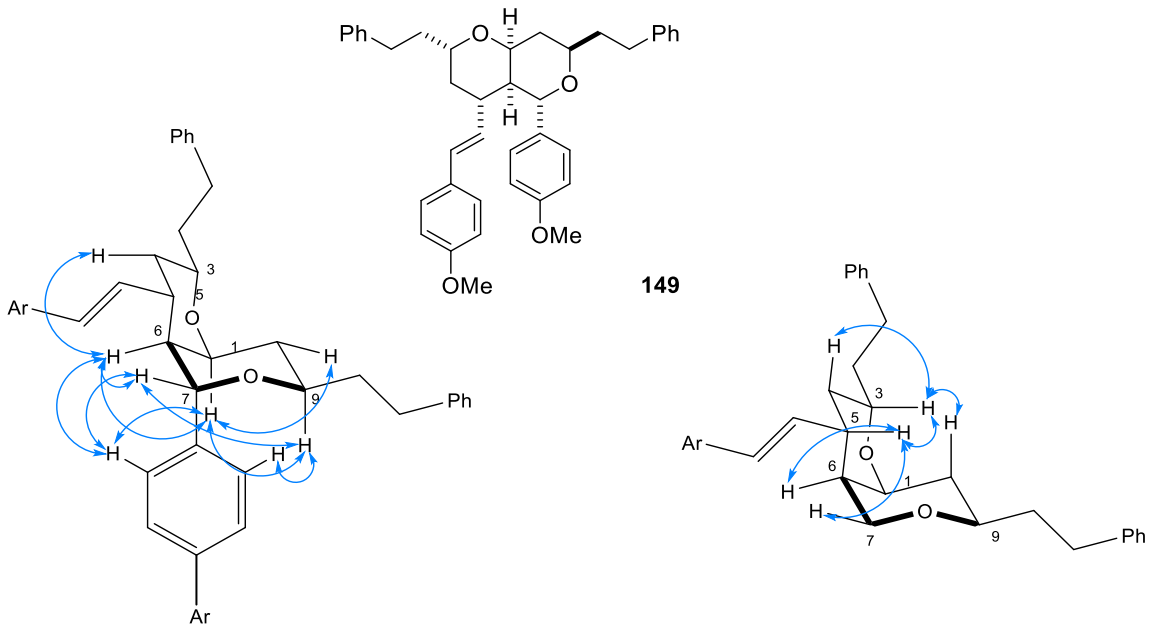


Figure 23. nOe correlations (blue) of analogue **149**

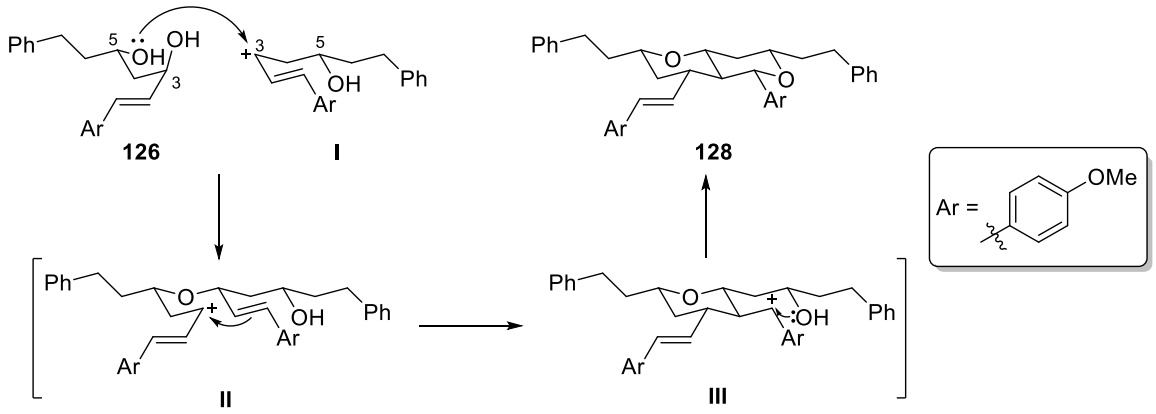
A further product **149** was also assembled on a *cis*-fused bicyclic framework deduced from the coupling (*J* 5 Hz) of the protons 1-H and 6-H and their nOe correlation. Interestingly, while the side chains at C-3, C-5 and C-9 are equatorial with 3-H, 5-H and 9-H showing vicinal axial-axial couplings (*J* 11-12 Hz), the 7-phenyl group is axial with 7-H appearing as a broad singlet at δ 5.15. The presence of nOe correlations of 7-H, 1-H, 10-H_{eq} and 6-H with the aromatic ring are in accord with the C-7 phenyl group being axial. Furthermore, this proposed structure was supported by nOe correlations among 3-H, 5-H and 10-H_{ax} revealing their co-axial relationship.

In conclusion, it is evident that more diastereomers are formed when using racemic diol **126**, eight compounds (Scheme 43) were isolated compared to five when diol **(+)-126** was used (Scheme 42). Additionally, the yield of those compounds that originate from coupling the two

enantiomers of the starting material increased when using racemic diol **126** and those coming from the same enantiomer significantly decreased.

1.3.8 Proposed reaction mechanism

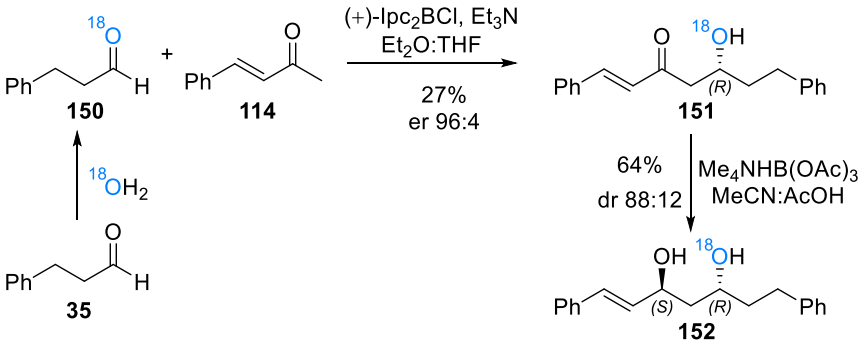
Results from the studies described herein using substrates with electron-rich and electron-deficient aromatic rings (pg. 29), combined with the array of products formed (pg. 34) are in accord with the proposed mechanism for the formation of the dimeric diarylheptanoids illustrated in Scheme 44 for the generation of the major diastereomer **128**. Loss of the allylic hydroxyl group from diol **126** gives carbocation **I** stabilised by the aromatic ring. Reaction of diol **126** with **I** couples the two molecules together generating a further intermediate **II**, then intramolecular attack leads to formation of the carbon-carbon bond and secondary carbocation **III** again stabilised by the aromatic ring. Finally, cyclisation generates the bicyclic product **128**. Whilst the *trans*-fused rings with all equatorial side chains **128** is preferred, other diastereomers may arise by non-stereoselective attack on the carbocationic intermediates (Scheme 44).



Scheme 44. Proposed mechanism for formation of dimeric diarylheptanoids

An interesting feature of the proposed mechanism is that the allylic alcohol at C-3 must be lost selectively from the diols in the coupling process, thus both oxygens in the bicyclic heterocycles will originate from 5-hydroxyl group of starting diol **126**. To verify this proposal, we used an oxygen-18 labelling approach where the site of isotopic label could be tracked by ^{13}C NMR spectroscopy. Risley and Van Etten[68] have reported that an ^{18}O-isotopic label in organic compounds results in an upfield shift in the ^{13}C NMR signal attach to the ^{18}O, the magnitude of which is dependent on the type of compound, in the case of alcohols a shift of *ca.* 0.02 ppm is expected. As such a small shift is to be detected and so ideally the substrate will have <90% incorporation of oxygen-18 so that two signals can be detected in the ^{13}C-NMR spectrum.

Thus, 3-phenylpropanal **35** was labelled to about 50% incorporation by exchange with oxygen-18 labelled water (Scheme 45). Then, [^{18}O]-phenylpropanal **150** and (*E*)-4-phenyl-3-buten-2-one **114** were treated with Et_3N and (+)-Ipc_2BCl to produce [^{18}O]-hydroxyketone **151** in 27% yield and 96:4 *er*, as determined by chiral HPLC. Directed reduction of **151** using $Me_4NHB(OAc)_3$ produced [^{18}O]-*anti*-diol **152** with 88:12 *dr* and in 90% yield. The signal assigned to C-5 in the ^{13}C-NMR spectrum is shown in Figure 24, in which two signals are apparent, one due to ^{13}C-^{16}O (δ 69.07) and an upfield signal from ^{13}C-^{18}O (δ 69.04).



Scheme 45. Synthesis of [^{18}O]-*anti*-diol **152**

[^{18}O]-Diol **152** was treated with TMSOTf at 0 °C for 1.5 h and after standard work-up, column chromatography and further HPLC purification, dimeric product [^{18}O]-**153** was isolated in 8% yield. The ^{13}C NMR spectrum of **153** clearly showed that the signals assigned to all four oxygenated carbons in the rings C-1 (δ 79.13), C-3 (δ 75.77), C-7 (δ 83.39), C-9 (δ 75.02), retained the oxygen-18 label, consistent with the proposed mechanism of dimerisation (Figure 24).

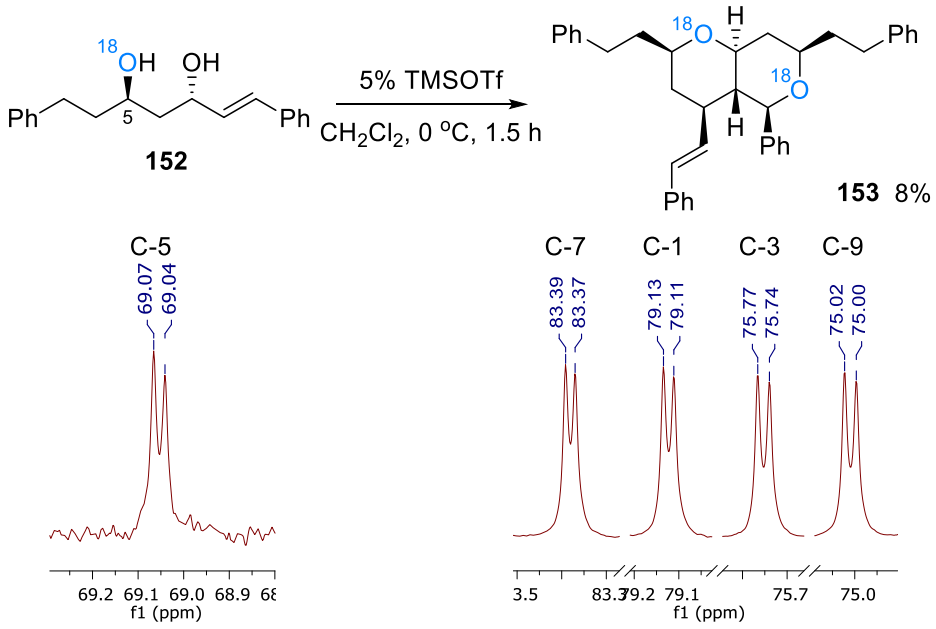
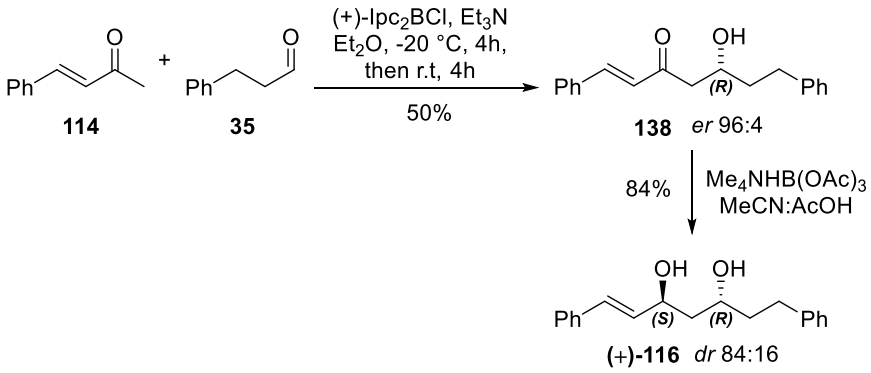


Figure 24. ^{13}C NMR showing the C-1, C-3, C-7 and C-9 of **153** recorded in $CDCl_3$

1.3.9 Synthesis and acid-mediated cyclisation of (+)-*anti*-diol 116

To investigate if the acid-mediated cyclisation of the enantiopure material with phenyl groups, rather than the electron-rich *p*-methoxyphenyl group, would form the same group of compounds, (+)-*anti*-diol **116** was synthesised. Enone **114** and aldehyde **35** were reacted with (+)-Ipc_2BCl and Et_3N producing β-hydroxyketone **139** in 50% yield with 96:4 *er* as determined by chiral HPLC (Figure 25). $Me_4NHB(OAc)_3$ reduction of **138** gave (+)-*anti*-diol **116** in 84:16 *dr* as determined by ^1H NMR spectroscopy (Scheme 46).



Scheme 46. Synthesis of (+)-*anti*-diol **116**

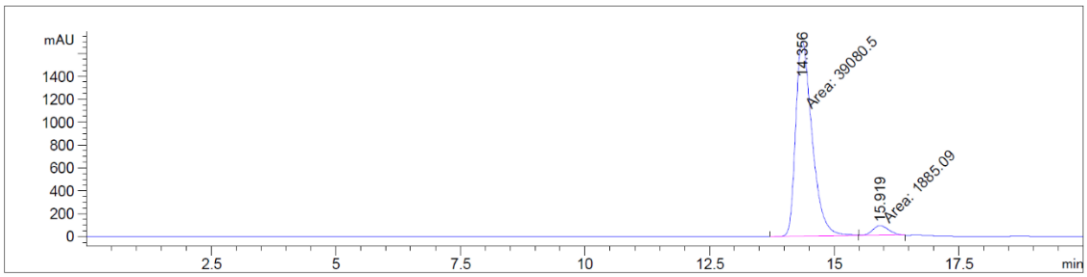
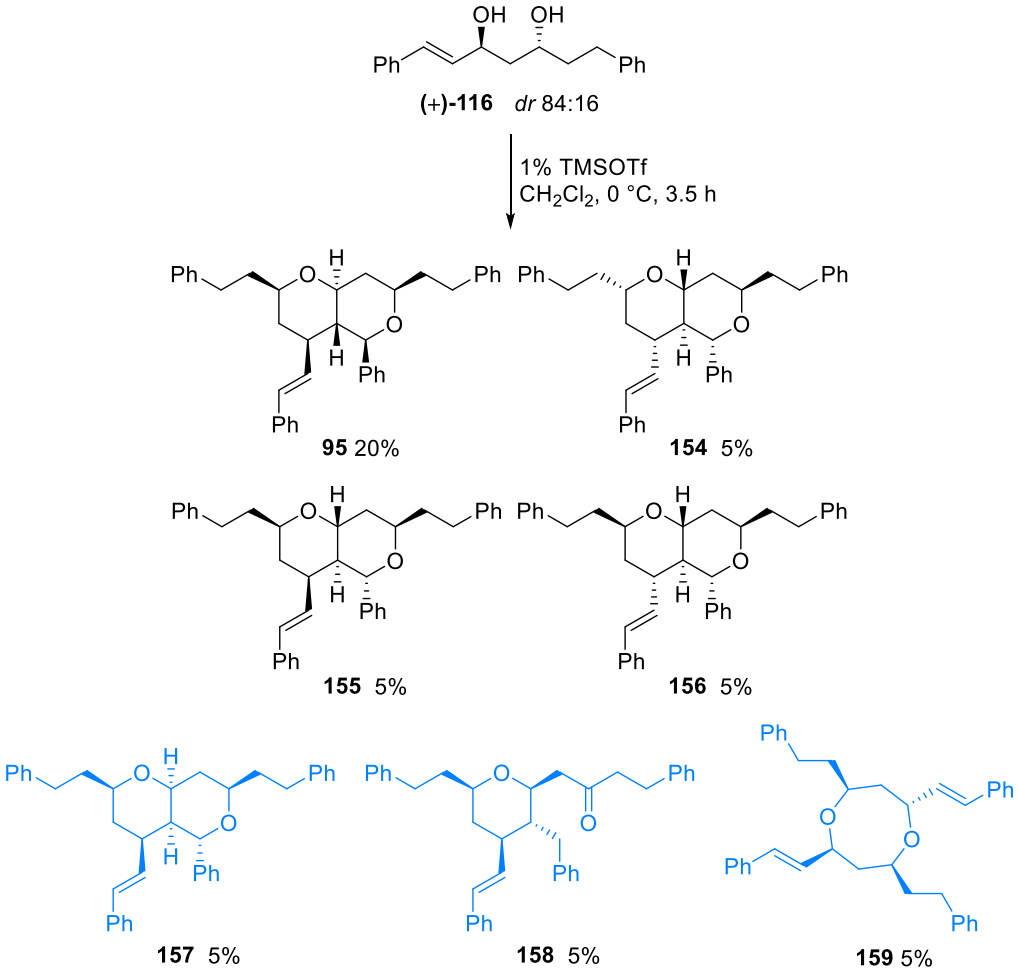


Figure 25. Chiral HPLC trace of enantioenriched hydroxyketone **138**

(+)-*Anti*-diol **116** was treated with 1% TMSOTf at 0 °C with stirring for 3.5 hours (Scheme 47). After standard work-up, the reaction mixture was purified by column chromatography giving four mixed fractions which were further purified using normal phase HPLC. Seven compounds **95** and **154**-**159** were isolated.



Scheme 47. Acid-mediated cyclisation of (+)-*anti*-diol **116**

Compound **95** is an analogue of blepharocalyxin D with a *trans*-2,8-dioxa[4.4.0]bicyclodecane core and the four side chains in equatorial position. Racemic **95** was synthesised earlier in this project (Scheme 21), therefore its structure and relative configuration is known. Analogues of compound **154**-**156** have been already synthesised differing only in the aromatic ring on the C-5 and C-7 side chains. Compounds **154**-**156** contain a phenyl group while analogues **143**-**145** bear a *p*-methoxyphenyl group. Thus, these compounds were readily characterised by comparison of their ^{1}H and ^{13}C NMR spectra (Figure 26, Figure 27 & Figure 28).

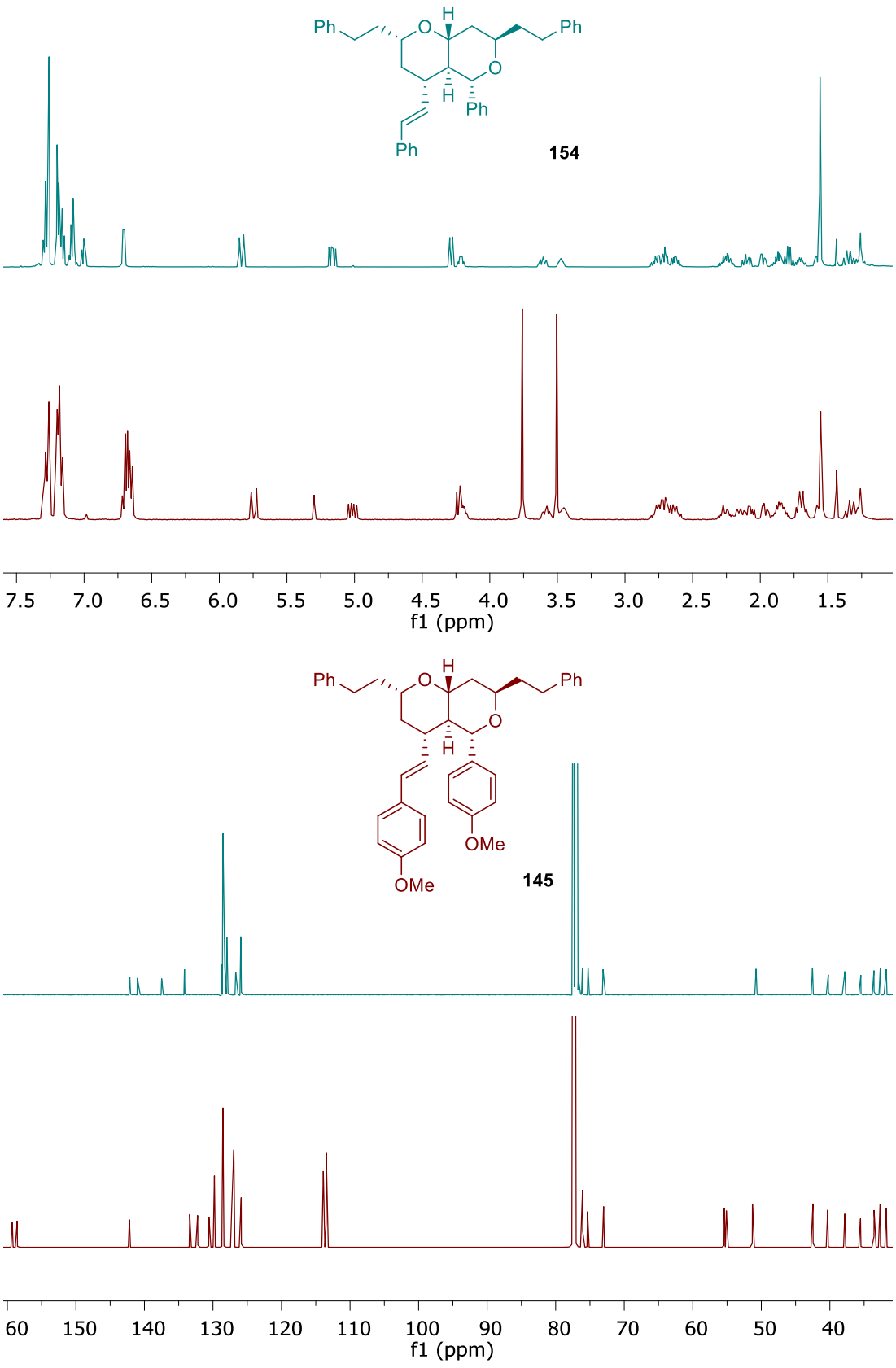


Figure 26. ^{1}H and ^{13}C NMR spectra of analogue **145** and isolated compound **154**

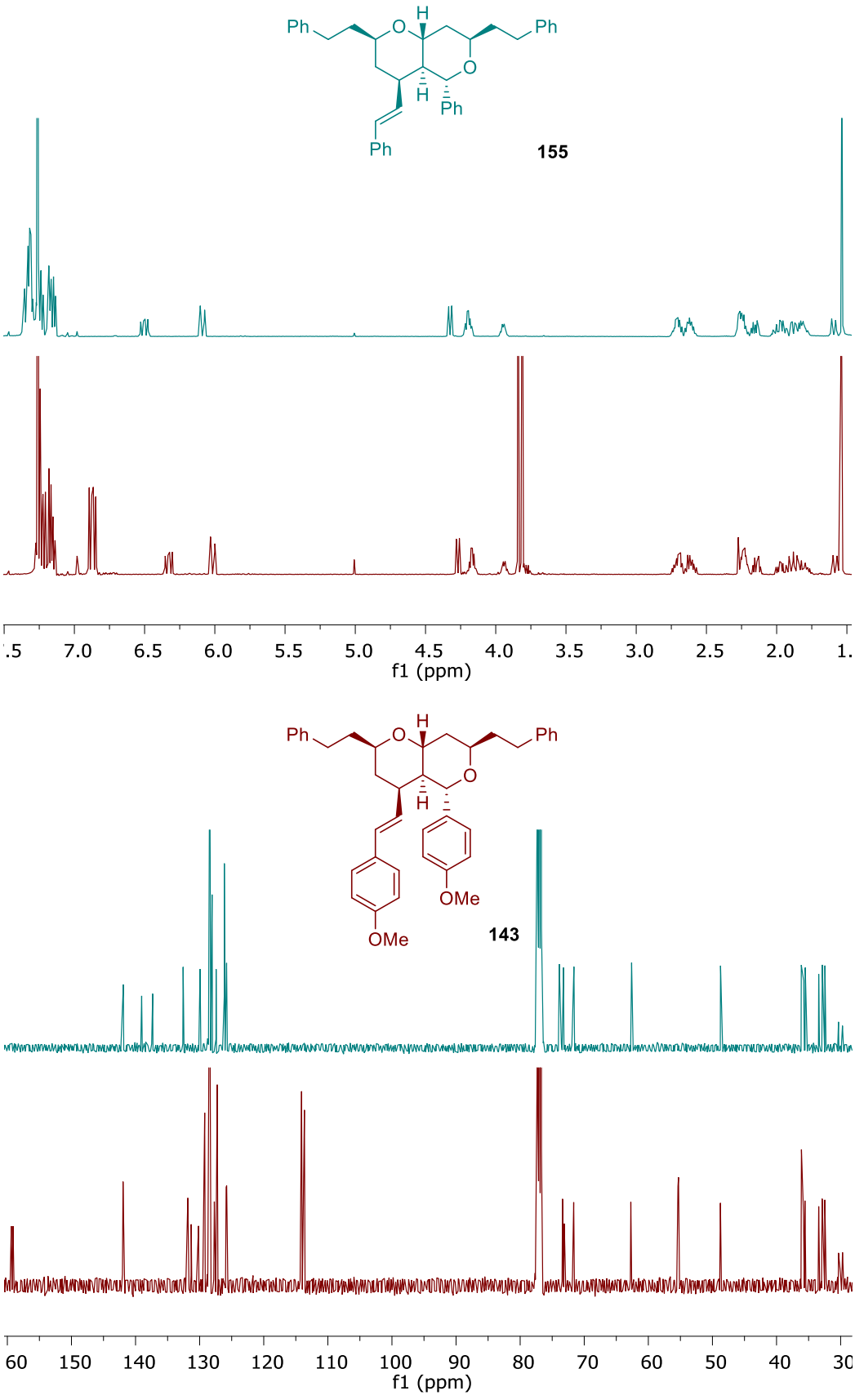


Figure 27. ^{1}H and ^{13}C NMR spectra of analogue **143** and isolated compound **155**

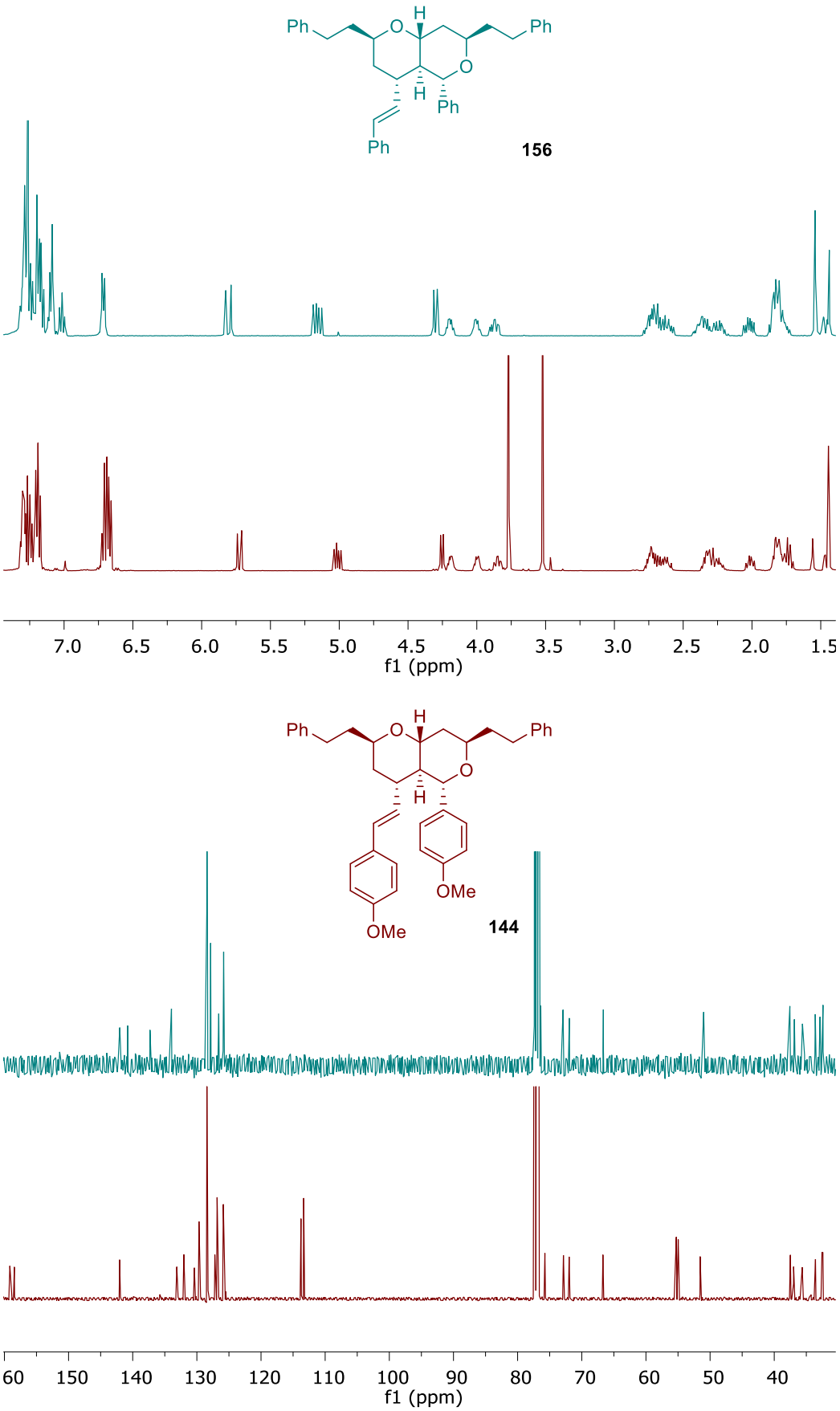


Figure 28. ^{1}H and ^{13}C NMR spectra of analogue **144** and isolated compound **156**

The three new compounds **157**-**159** were isolated and characterised using HRMS and extensive ^{1}H and ^{13}C NMR spectroscopy including nOe. All of them have the same molecular formula of $C_{38}H_{40}O_2$, but in this case only compound **157** had similar ^{1}H and ^{13}C NMR spectra to previous analogues of blepharocalyxin D.

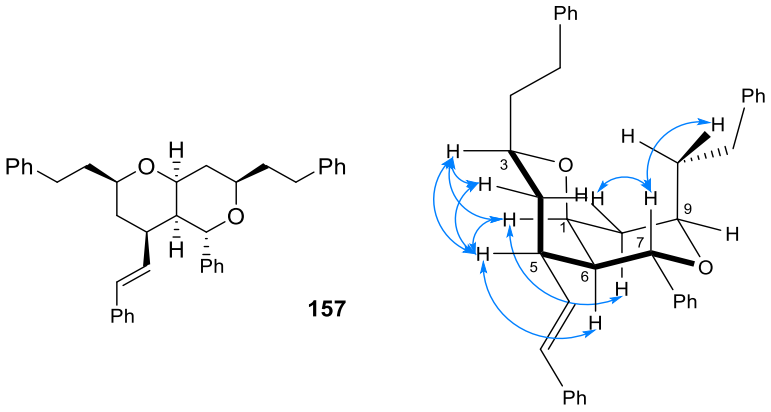


Figure 29. 3D structure of dimeric diarylheptanoid **157** with diagnostic nOe correlations (blue).

Compound **157** was assembled on a *cis*-fused ring bicyclic framework deduced from the *cis* coupling (*J* 3 Hz) of 6-H with 1-H. The side chains at C-3, C-5 and C-7 are equatorial with 3-H, 5-H and 7-H showing vicinal axial-axial couplings (*J* 11 Hz). This proposed structure was supported by nOe correlations among 1-H, 3-H, 5-H and 6-H revealing their co-axial relationship. There were correlations between 7-H, 4-H_{ax} and 9-CH_2 confirming the co-axial relationship of 7-H, 4-H_{ax} and the side chain at C-9.

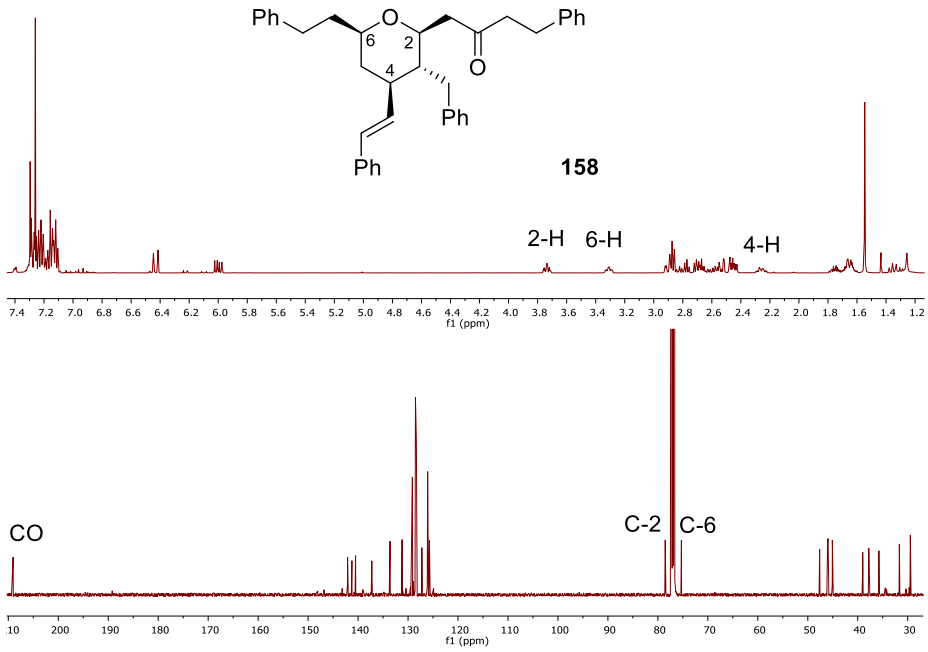


Figure 30. ^{1}H and ^{13}C NMR spectra of tetrahydropyran **158**

Interestingly, one of the new compounds isolated was tetrahydropyran **158**. Its ^{1}H NMR spectrum showed only two signals (δ 3.74 & δ 3.31) assigned to CHO, and its ^{13}C NMR spectrum showed the two signals (δ 78.5 & 75.3) characteristic for carbon next to oxygen. Additionally, a characteristic signal at δ 209 for a carbonyl group (CO) was observed (Figure 30).

Tetrahydropyran **158** has a chair conformation with the four side chains at C-2, C-3, C-4 and C-6 all equatorial as determined from the vicinal *trans* coupling (*J* 10-12 Hz) of 2-H, 3-H, 4-H, 5-H_{ax} and 6-H. This conclusion was supported by nOe correlations among 2-H, 4-H and 6-H revealing their co-axial relationship. Whilst, 3-H and 5-H_{ax} showed nOe correlation in accord with the side chain at C-3 being equatorial.

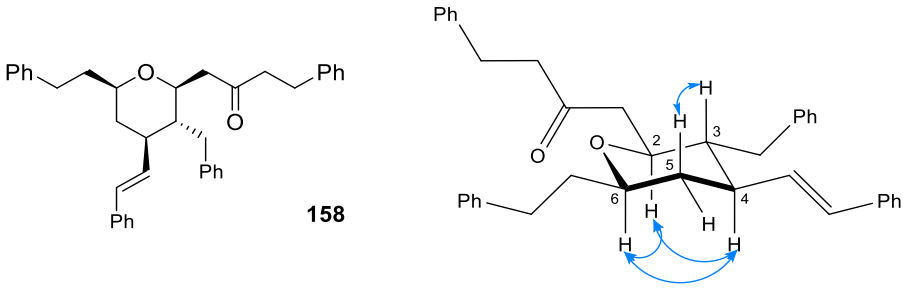
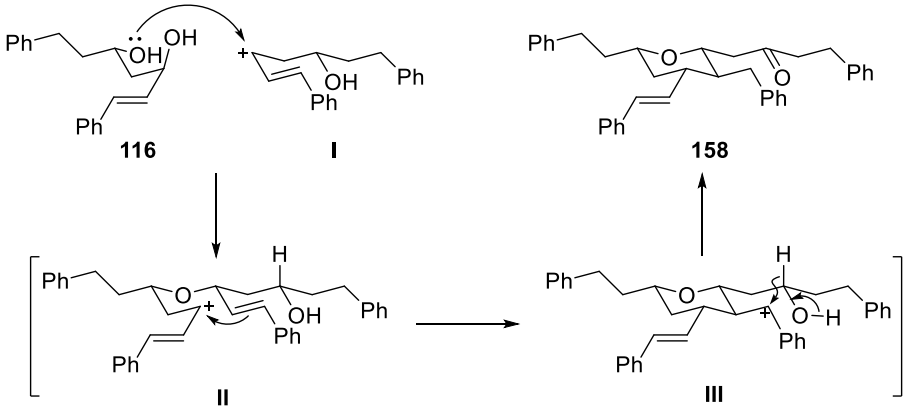


Figure 31. 3D structure of tetrahydropyran **158** with diagnostic nOe correlations (blue).

The proposed mechanism for the formation of tetrahydropyran **158** is shown in Scheme 48. Loss of the allylic hydroxyl group from diol **116** gives carbocation **I**. Reaction of diol **116** with **I** couples the two molecules together generating a further intermediate **II**, then intramolecular attack leads to formation of the carbon-carbon bond and secondary carbocation **III**. Finally, a 1,5-hydride shift occurs generating tetrahydropyran **158** (Scheme 48).



Scheme 48. Proposed mechanism for the formation of tetrahydropyran **158**

The final isolated product **159** has a ^{1}H NMR spectra which resembled a 1:1 mixture of diastereomers of starting diol **116**, but its molecular formula was that of a dimer. Analysis of the 1D and 2D NMR spectrum revealed a 1,5-dioxocane structure (Figure 32).

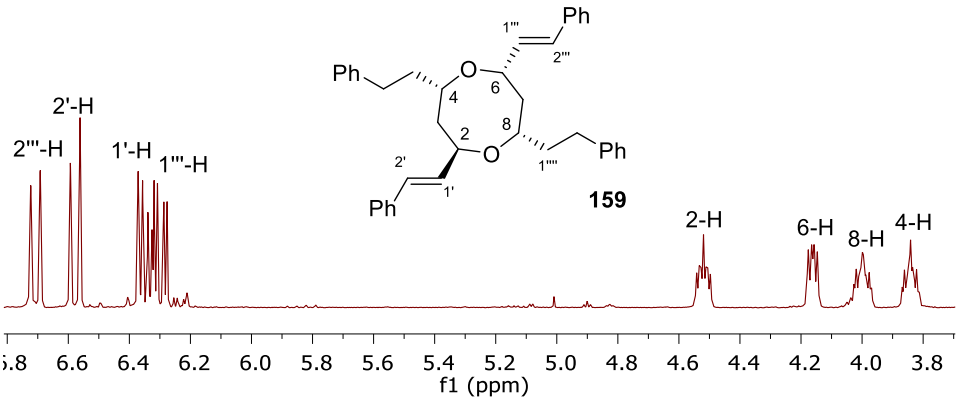


Figure 32. Diagnostic signals of the ^{1}H spectrum of dimer **159**

Dimer **159** adopts the conformation shown in Figure 33 with the side chains at C-2, C-4 and C-6 in equatorial positions and C-8 axial. This was determined from the magnitude of the vicinal coupling constants (*J* 10-11 Hz) of 2-H with 3-H_{ax} and of 6-H with 7-H_{ax} and supported by nOe correlations shown in Figure 33. There were correlations between 7-H_{ax} and 2-H which also correlates with the 1''''-H (the side chain at C-8) as well as among 3-H_{ax}, 6-H and 4-H revealing their co-axial relationship.

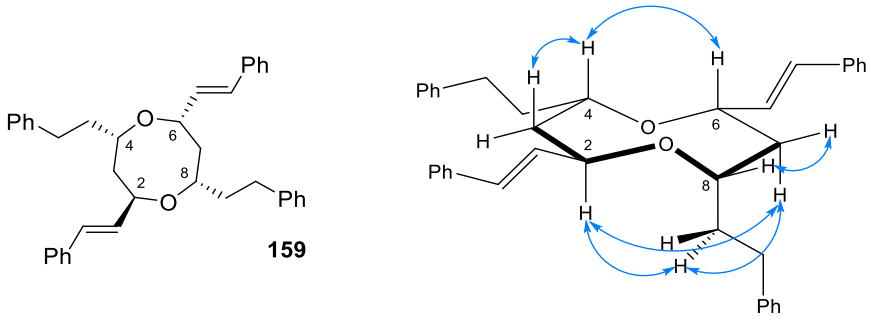
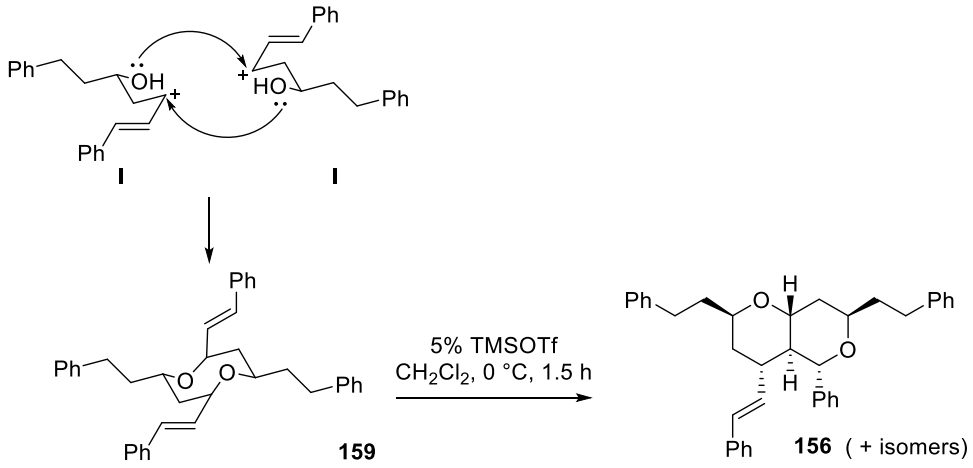


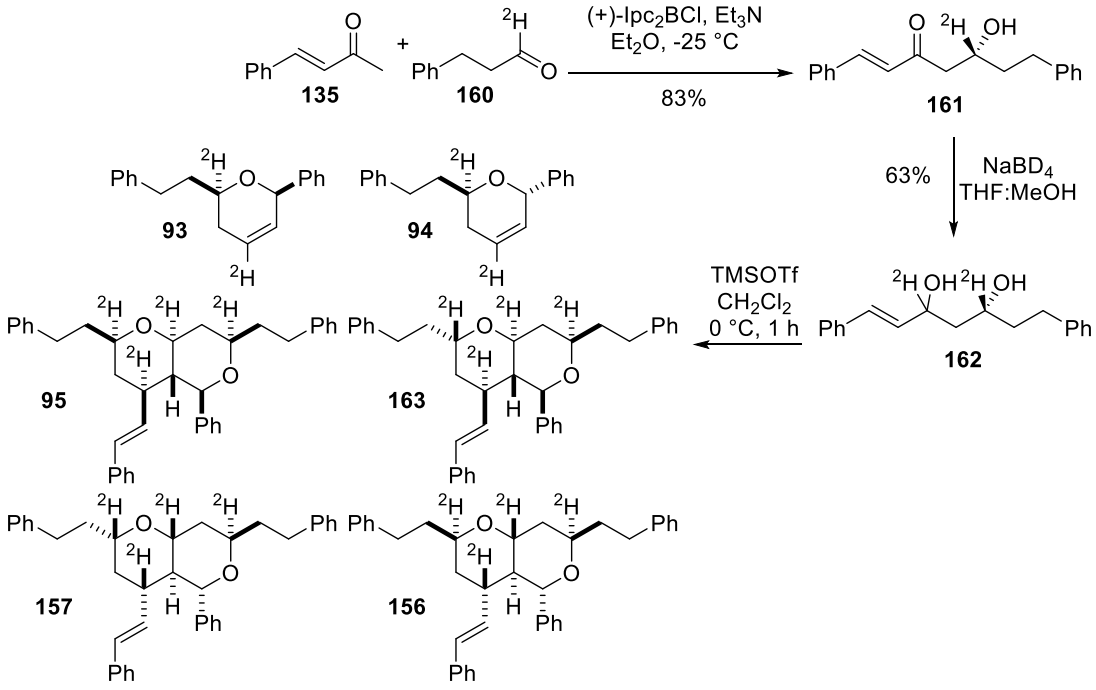
Figure 33. 3D structure of 1,5-dioxocane **159** with diagnostic nOe correlations (blue).

The formation of 1,5-dioxocane **159** could be explained from coupling of two molecules of the carbocationic intermediate **I** which is formed from the loss of the allylic hydroxyl group from diol **116**. Whilst shown as a concerted process it is likely to be stepwise. Eight-membered ring **159** was treated with 5% TMSOTf at 0 °C for 1.5 h producing a mixture of dimeric diarylheptanoids where the major component was diastereomer **156** (Scheme 49).



Scheme 49.Proposed mechanism for formation of **159** and its acid-mediated reaction

To investigate the proposed mechanisms of formation of the minor components found in the crude reaction mixture, [3,5-$^2H_2$]-diol **162** was synthesised as a substrate in the standard cyclisation reaction. [^{2}H]-Aldehyde **160** and enone **135** were reacted with (+)-Ipc_2BCl and Et_3N to produce [5-^{2}H]-hydroxyketone **161** which was reduced to [3,5-$^2H_2$]-diol **162** using NaB^2H_4 in THF:MeOH (Scheme 50). [3,5-$^2H_2$]-Diol **162** was treated with TMSOTf in dichloromethane for 1 h at 0 °C. The crude mixture was separated using HPLC giving [3,5-$^2H_2$]-*anti*- and [3,5-$^2H_2$]-*syn*-dihydropyrans **93** and **94** and four dimeric [1,3,5,9-$^2H_4$]-diarylheptanoids **95**, **156**, **157** & **163**.



Scheme 50. Synthesis of [3,5-$^2H_2$]-diol **162** and its acid-mediated cyclisation

In the case of the dimeric diarylheptanoids the ^{1}H NMR signals assigned to 1-H, 3-H, 5-H and 9-H in the non-labelled product **95** were absent in **[1,3,5,9-$^{2}H_4$]-95**. (Figure 34) Similarly in dihydropyran **93** the signals assigned to 3-H and 5-H were absent in the [3,5-$^{2}H_2$]-dihydropyran **93**. (Figure 35)

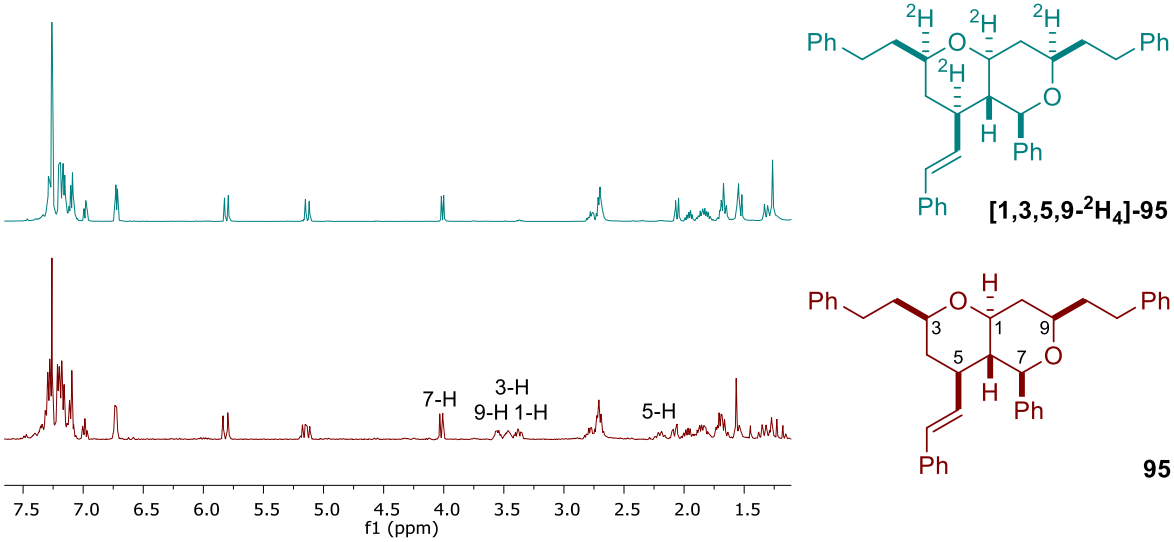


Figure 34. ^{1}H NMR spectra of [1,3,5,9-$^{2}H_4$]-diarylheptanoid **95** and diarylheptanoid **95**

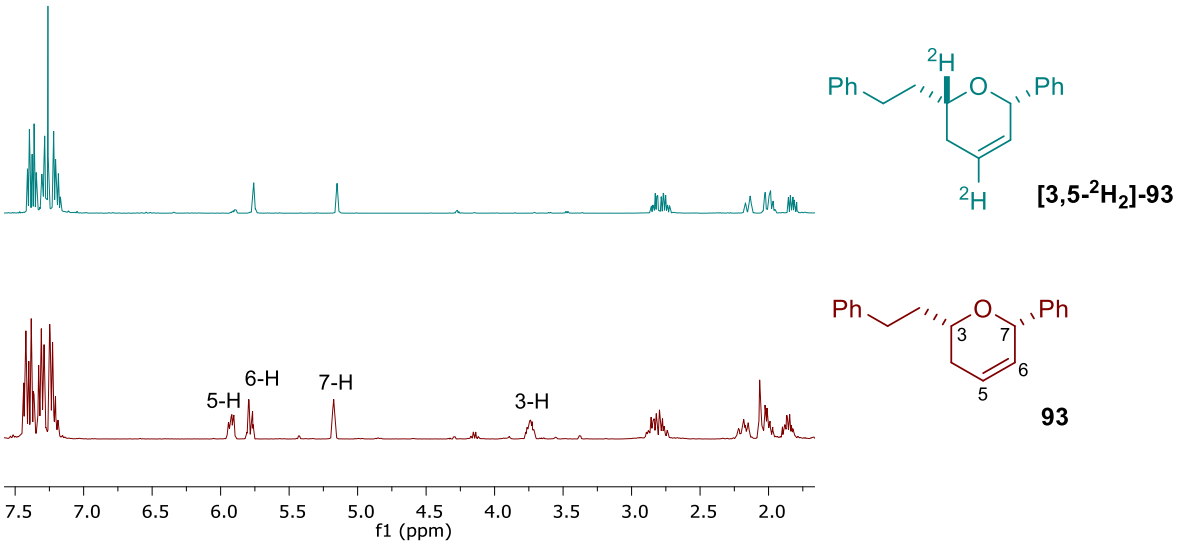
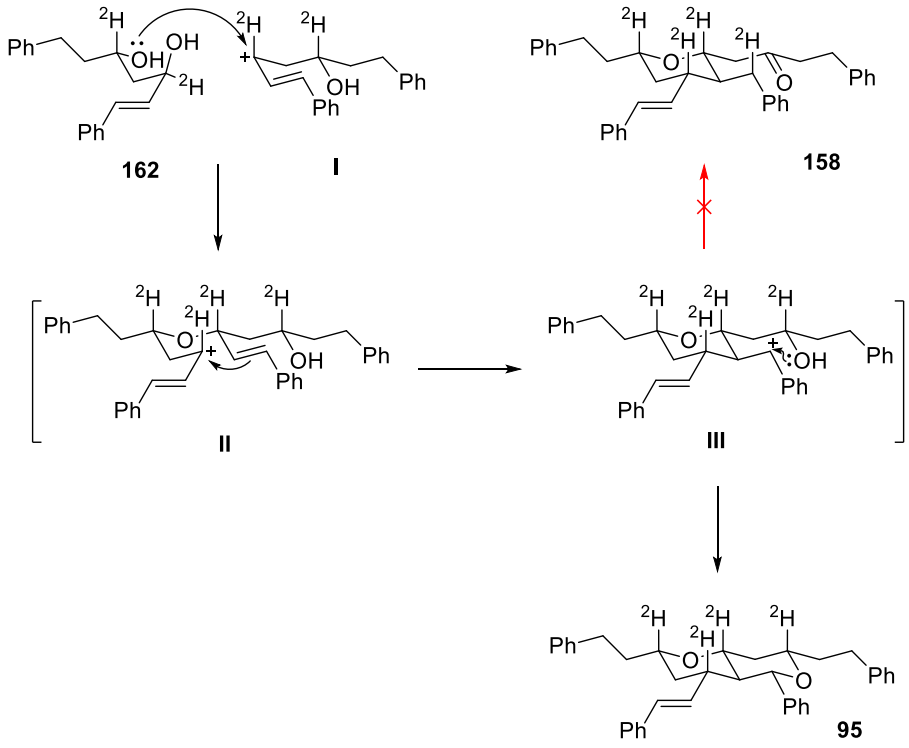


Figure 35. ^{1}H NMR spectra of [3,5-$^{2}H_2$]-dihydropyran **93** and dihydropyran **93**

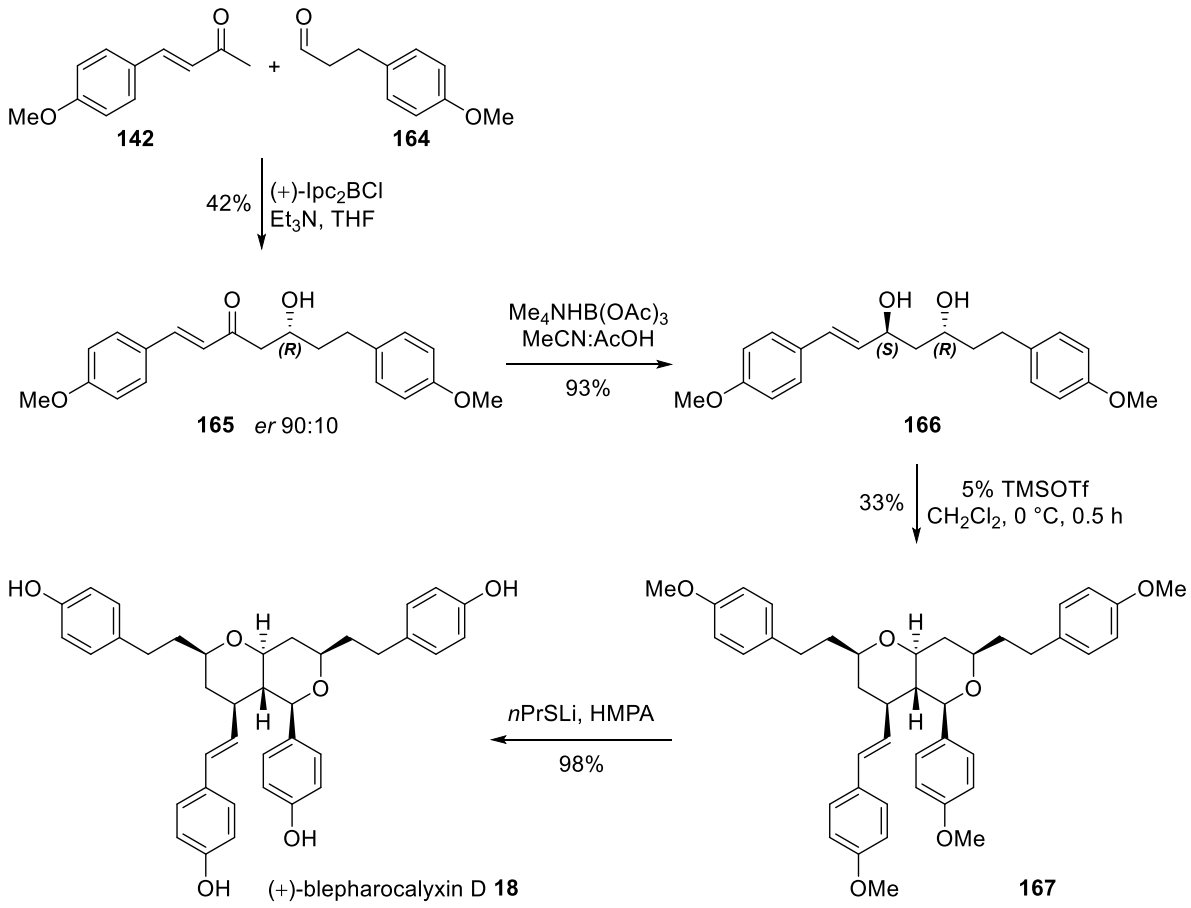
Interestingly, neither of the minor components **158** and **159** was observed in the reaction mixture. In the case of tetrahydropyran **158**, we proposed that intermediated **III** required a 1,5-hydride shift to generate the ketone. Hence a possible explanation is that, as the carbon-deuterium bond is stronger than the C-H bond this pathway is no longer favoured, so tetrahydropyran **158** was not formed.



Scheme 51. Proposed mechanism of cyclisations

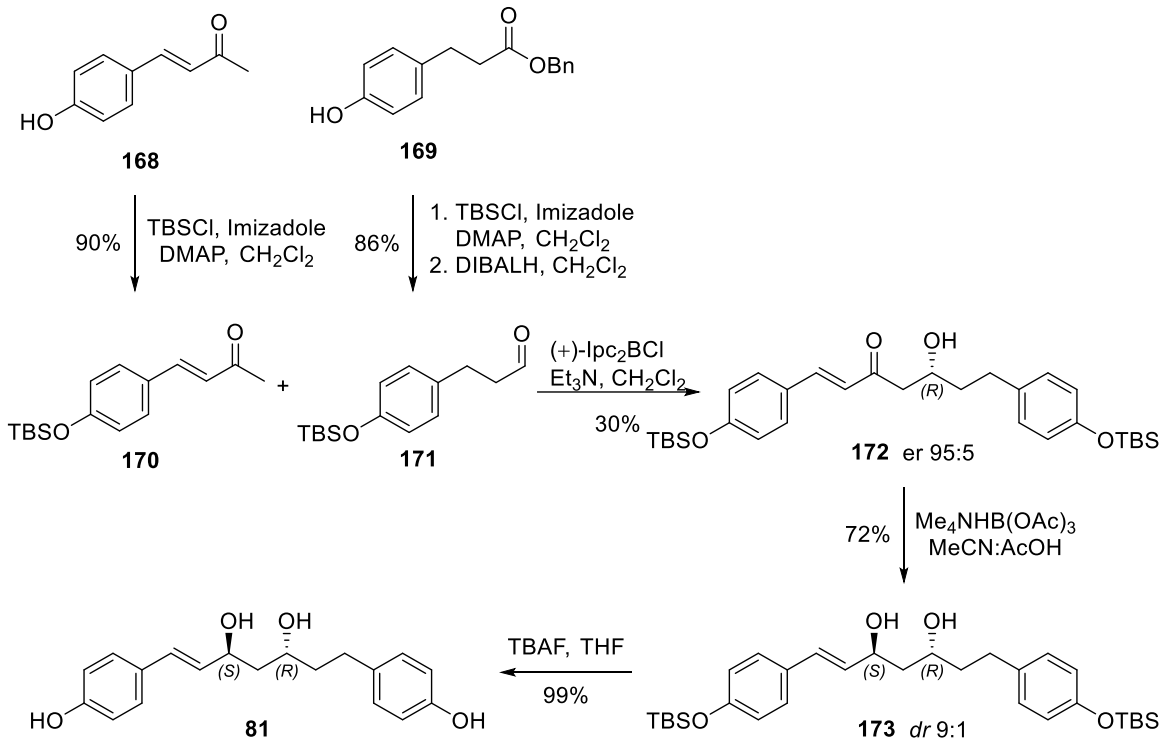
1.3.10 Total synthesis of (+)-blepharocalyxin D

Having developed a concise approach for the synthesis of dimeric diarylheptanoids, it was then applied to the synthesis of (+)-blepharocalyxin D. This was of interest to compare its bioactivity with the natural product (–)-blepharocalyxin D (Scheme 52). The required substrate **166** for the key cyclisation was prepared in 2 steps *via* an aldol reaction of *p*-methoxyphenylpropanal **164** and *p*-methoxyphenyl butanone **142** using (+)-Ipc_2BCl and Et_3N producing β-hydroxyketone **165** in 42% yield with 90:10 *er*. Subsequent directed reduction using $Me_4NHB(OAc)_3$ gave *anti*-diol **166** in 93% yield. Treatment of **166** with TMSOTf produced bicyclic compound **167** in 33% yield which was deprotected using LiSPr/HMPA to give (+)-blepharocalyxin D in 98% yield. Thus, the target compound was synthesised in 4 steps from simple starting materials **142** and **164** in 13% overall yield. The synthetic sample of (+)-blepharocalyxin D gave an optical rotation value of $[\alpha]_D$ +80.3 (*c.* 0.7 MeOH) in accord for it being the enantiomer of the natural product with $[\alpha]_D$ –90.4 (*c.* 0.32 $CHCl_3$).



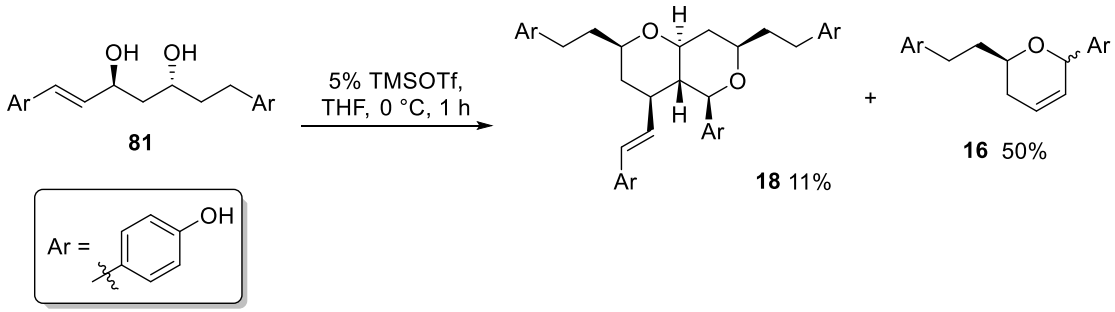
Scheme 52. Total synthesis of (+)-blepharocalyxin D

At the beginning of this project a proposed biosynthesis of blepharocalyxin D (Scheme 18) was described with diol **81** as the natural precursor to blepharocalyxin D. Thus, to investigate if this compound would react to form blepharocalyxin D, we embarked in the synthesis of diol **81**. Hence, following the concise approach that had been developed, the two components required for the aldol reaction were synthesised (Scheme 53). *p*-Hydroxybenzaldehyde and acetone were treated with a 10% solution of NaOH producing the required enone **168** in 55% yield, which was reacted with TBSCl, imidazole and DMAP to produce the corresponding silyl ether **170** in 90% yield. To synthesise the required aldehyde **171**, benzyl ester **169** was protected with TBSCl and imidazole to give the corresponding silyl ether and subsequent DIBALH reduction at −78 °C gave the required aldehyde **171** in 86% yield. Then, silyl ethers **170** and **171** were coupled with (+)-Ipc_2BCl and Et_3N giving β-hydroxyketone **172** in 30% yield with 95:5 *er*, as determined by chiral HPLC. Subsequent Evans-Saksena directed reduction produced diol **173** in 72% yield with 9:1 *dr*, as determined by ^1H NMR spectroscopy. Finally, deprotection of the TBS groups using TBAF gave the required precursor **81** in quantitative yield.



Scheme 53. Synthesis of diol **81**

Diol **81** was treated with 5% TMSOTf in THF for 1 h and after chromatography purification (+)-blepharocalyxin D was isolated in 11% yield (Scheme 54). Contrary to our standard dimerisation conditions, THF had to be used as the solvent as starting diol **81** was insoluble in dichloromethane. Inconveniently, this solvent favoured the production of dihydropyrans which were isolated in 50% yield. A 1:1 mixture of THF:CH_2Cl_2 was tested, but unfortunately no improvement was observed.



Scheme 54. Acid-mediated cyclisation of diol **81**

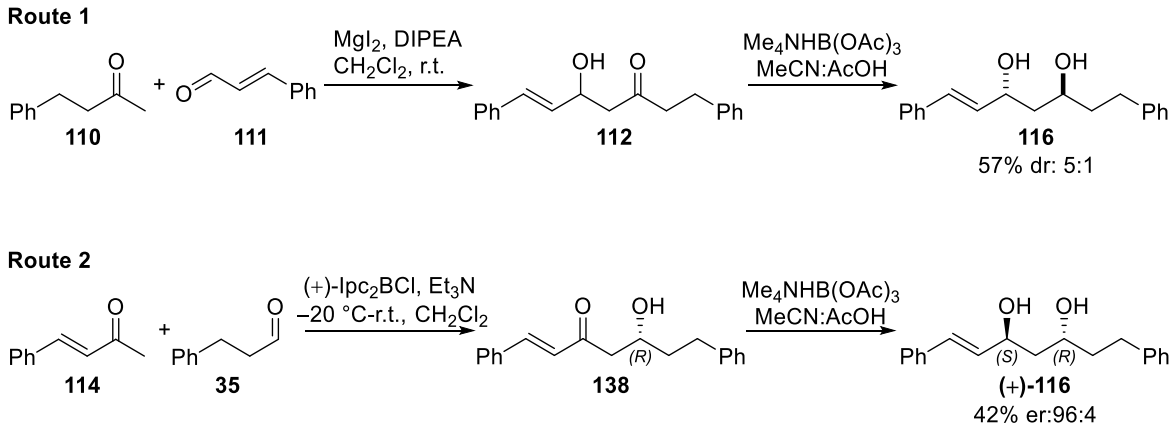
This reaction demonstrated that blepharocalyxin D and dihydropyrans can be formed from diol **81** as in the proposed biosynthesis described by Kadota and co-workers (Scheme 18, pg. 16).[22]

(+)-Blepharocalyxin D was tested for antiproliferative activity (by Summit Pharmaceuticals) and it proved to have moderate cytotoxic activity against HepG2 cell line with an IC_{50} of 48.5 µM. It is slightly less effective than (−)-blepharocalyxin D which gives an ED_{50} of 3.61 µM against 26-L5 carcinoma cells and 25.7 µM against human HT-1080 fibrosarcoma cells.

1.4 Conclusions

In conclusion, we have developed a bioinspired approach for the efficient synthesis of bicyclic heterocycles assembled on a 2,8-dioxabicyclo[4.4.0]decane core decorated with 4 side chains. The key atom economic step involves an acid mediated dimerisation of a linear dihydroxy-diarylheptanoid to produce two oxane rings and 4 new stereocentres in one pot. This route was used for the synthesis of (+)-blepharocalyxin D in 4 steps and 13% overall yield from simple starting material which is more efficient that previous published routes to blepharocalyxin D (Lee 17 steps, 0.9% yield and Cons & Willis 15 steps, 8% yield).

Four routes were developed for the synthesis of linear dihydroxy-diarylheptanoids, two of them being short and efficient. The first one, using MgI_2 as catalyst for an aldol reaction to produce β-hydroxyketone **112** then a directed reduction gave *anti*-diol **116** in 57% yield over the 2 steps (Scheme 55)**.** Although this synthesis is not enantioselective, it is simple to perform on a multigram scale. The second synthesis, using (+)-Ipc_2BCl as catalyst for the aldol reaction gives β-hydroxyketone **138** with 96:4 *er* which after stereoselective reduction gives diol **(+)-116** in 42% overall yield over the two steps.



Scheme 55. Two-step approaches for the synthesis of linear diarylheptanoids **116** and **(+)-116**

These routes were used in the synthesis of several dihydroxy-diarylheptanoids with electron-deficient and electron-rich aromatic rings (Figure 36).

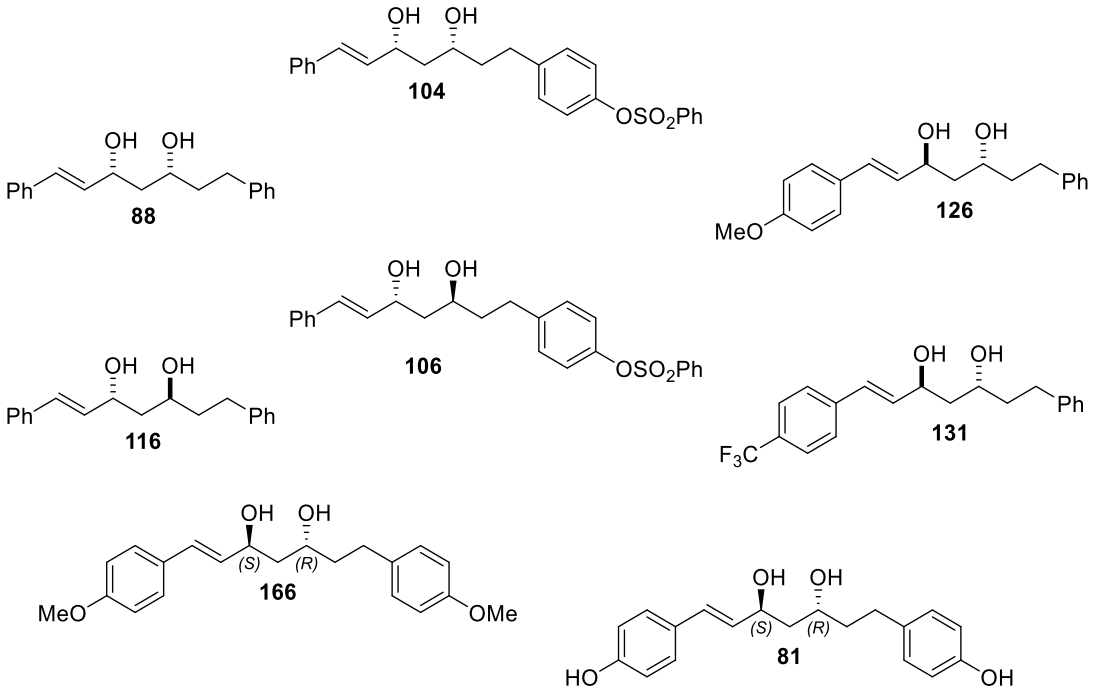
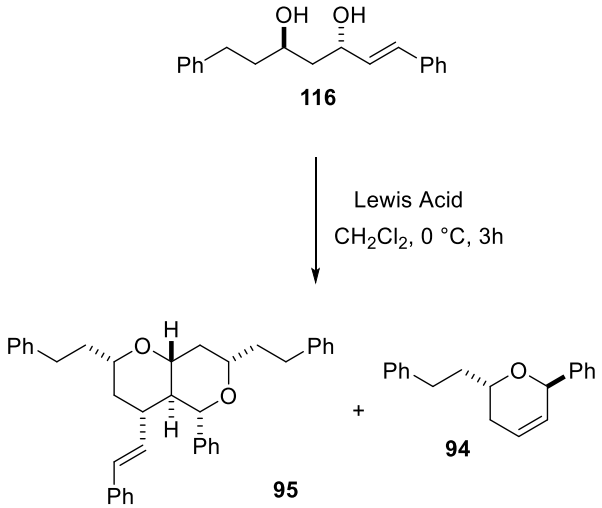


Figure 36. Synthesised dihydroxy-diarylheptanoids

The conditions for the key dimerisation step were optimised in terms of temperature, Lewis acid and solvent, concluding in the use of TMSOTf in CH_2Cl_2 at 0 °C. This dimerisation reaction produced mainly *trans*-2,8-dioxabicyclo[4.4.0]decanes, but dihydropyrans were also isolated in low yield (Scheme 56).



Scheme 56. Acid-mediated cyclisation of diol **116**

The key acid-mediated cyclisation of dihydroxy-diarylheptanoids was used for the synthesis of several analogues of blepharocalyxin D (Figure 37).

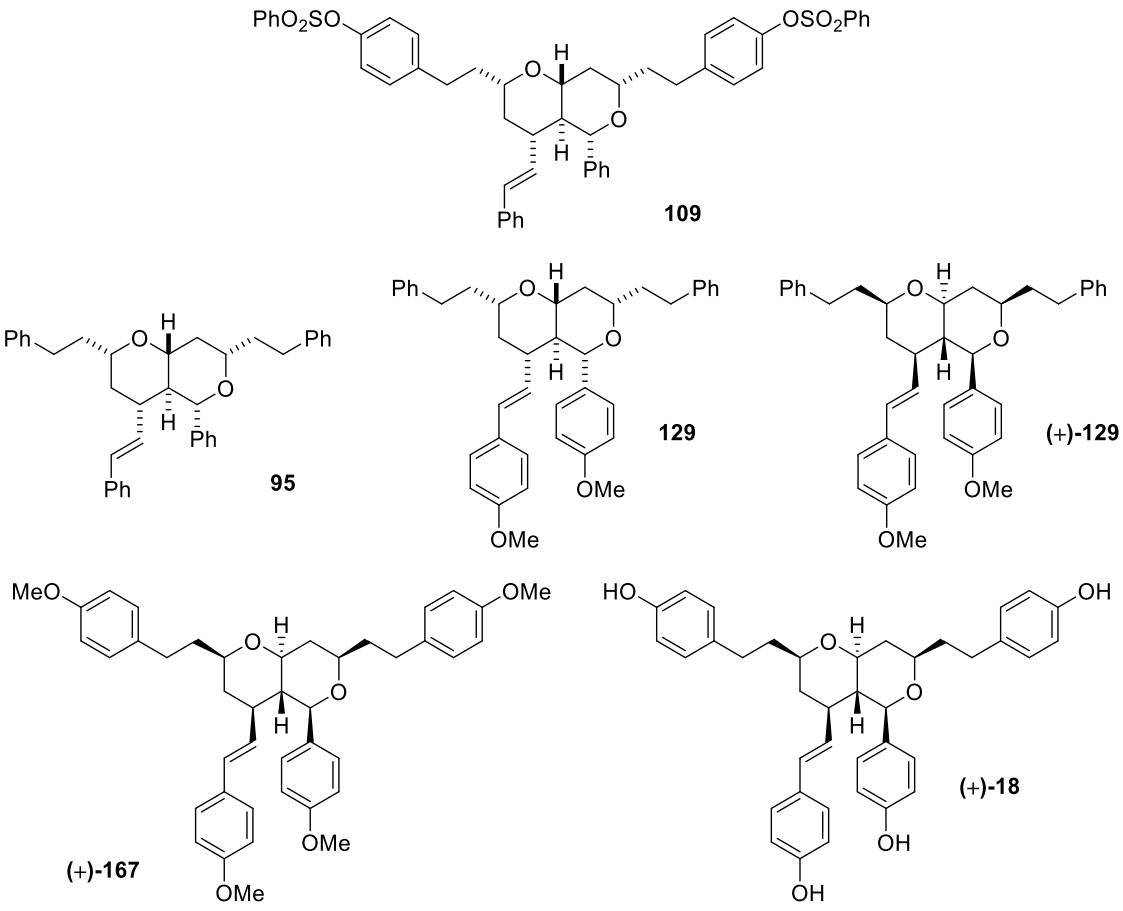
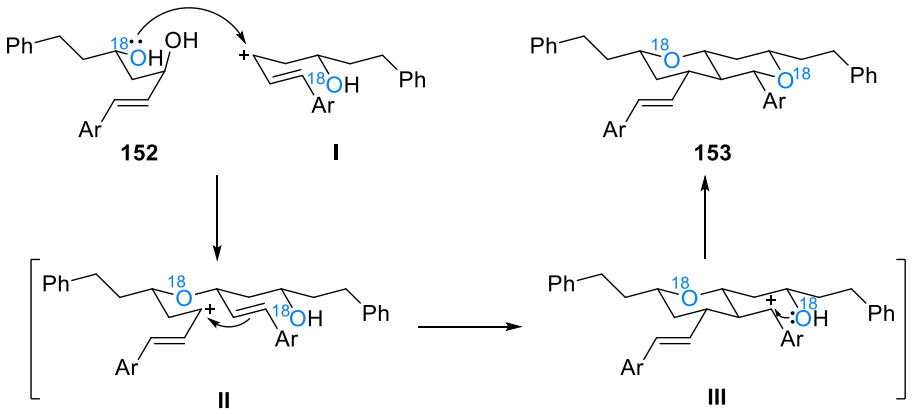


Figure 37. Synthesised analogues of blepharocalyxin D

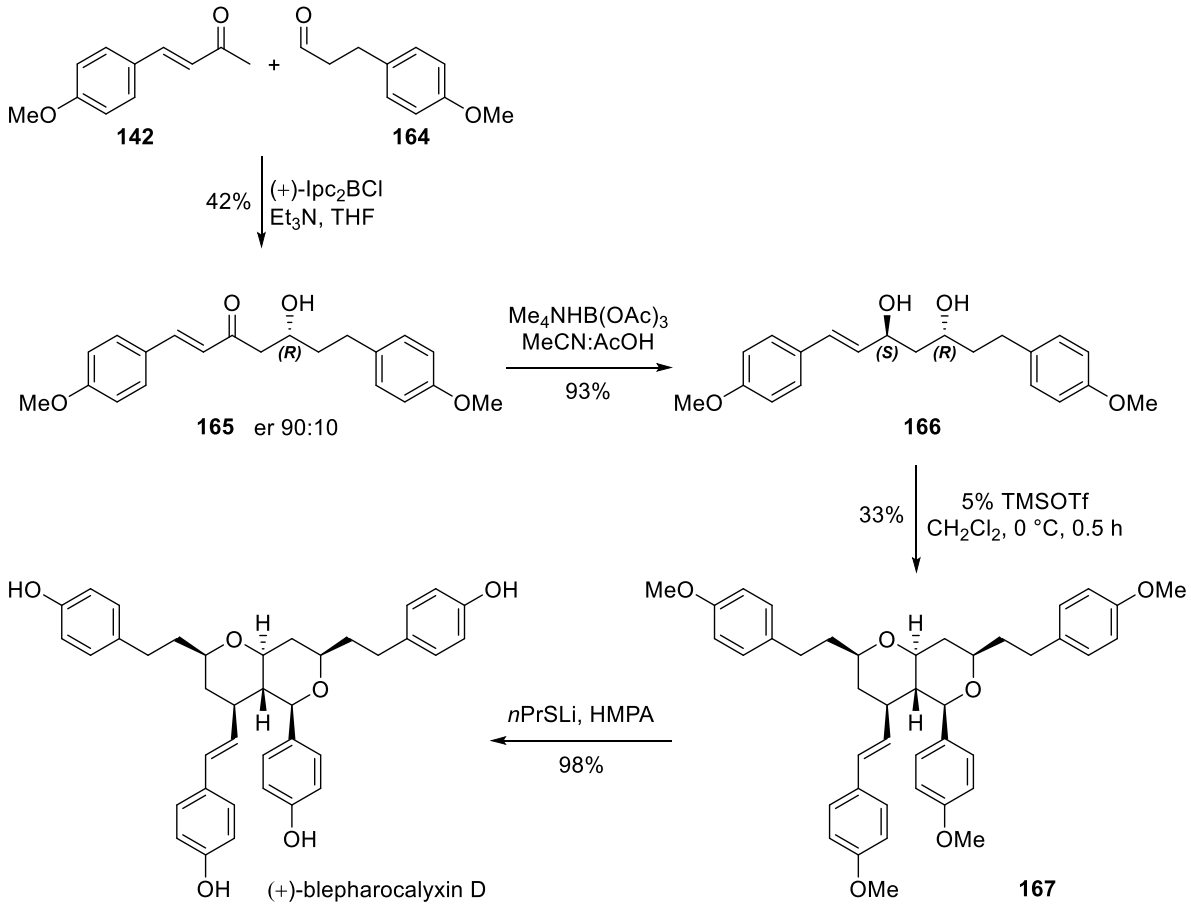
A mechanism for the reaction was proposed via a cascade involving carbocationic intermediates and verified by oxygen-18 labelling studies (Scheme 57), as well as deuterium labelling (Scheme 50).



Scheme 57. Oxygen-18 labelled proposed mechanism

The total synthesis of the enantiomer of the natural product have been achieved in 4 steps and 13% overall yield from simple starting materials, aldehyde **164** and enone **142**. The concise

approach significantly reduced the number of steps to such targets. Comparing with previous total syntheses of blepharocalyxin D where 17 and 15 steps[32,41] were required, it will give access to a library of dimeric diarylheptanoids for biological assessment (Scheme 58).



Scheme 58. Total synthesis of (+)-blepharocalyxin D.

2. Synthesis of Pleuromutilin Biosynthetic Intermediates

2.1 Introduction

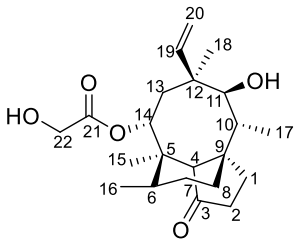
2.1.1 Use of pleuromutilins as antibiotics

Antibiotic resistance is an increasing problem worldwide, endangering the efficacy of antibiotics, which have transformed medicine and saved millions of lives.[69] The first cases of methicillin-resistant *Staphylococcus aureus* (MRSA) were identified in the United Kingdom in 1962 and in the United States in 1968.[70] Unfortunately, nowadays resistance has been observed to nearly all antibiotics that have been developed.[71] Although the pharmaceutical industry has introduced new antibiotics to solve the resistance problem, bacterial infections have again become a threat.[72] Among Gram-positive pathogens, a global pandemic of resistant *S. aureus* and Enterococcus species currently poses the biggest threat.[73] The global spread of drug resistance among common respiratory pathogens, including *Streptococcus pneumonia* and *Mycobacterium tuberculosis*, is epidemic.[73] MRSA infections can be very serious and are among the most frequently occurring of all antibiotic-resistance threats. *Enterococci* cause a wide range of illnesses, mostly among patients in hospitals or other health care settings, including bloodstream, surgical-site and urinary tract infections.[71] *S. pneumoniae* can cause serious and sometimes life-threatening infections. It is a major cause of bacterial pneumonia and meningitis, as well as bloodstream, ear and sinus infections.[74]

Rapidly emerging resistant bacteria threaten the extraordinary medical advances that have been achieved with antibiotics.[75] Hence, it is very important to develop new antibiotics for the treatment of bacterial infections, including resistant strains.

Pleuromutilin is a diterpene fungal metabolite which was first reported by Kavanagh in 1951.[76] It was isolated from two basidiomycetes species, *Pleurotus mutilis* (now known as *Clitopilus scyphoides)* and *Pleurotus passeckeranius* (now known as *Clitopilus passeckeranius*), although it has now been found to be produced by 11 different *Clitopilus* strains.[77] In the early 1960s structural elucidation studies were published giving the molecular formula of pleuromutilin as $C_{22}H_{34}O_5$ and assigning three of the five oxygen-bearing centres as two non-phenolic hydroxyl groups and one hindered carbonyl group.[78] Independent work by Arigoni[79] and Birch[80] culminated in publication of the full and correct structure of (+)-pleuromutilin and provided first insights into the biosynthesis. This work revealed the unique tricyclic diterpenoid core of pleuromutilin, which consists of fused 5-,6- and 8-membered rings and eight stereocentres. The

numbering of pleuromutilin shown in Figure 38 was described by Arigoni and has become convention throughout pleuromutilin chemistry. Further evidence for the structure was established by Bonavia[81] on the basis of X-ray and ORD data to establish the final stereochemistry.



(+)-Pleuromutilin **174**

Figure 38. Structure of (+)-pleuromutilin with standard numbering

Initial antibacterial studies by Kavanagh[82] showed pleuromutilin was active against Gram-positive bacteria, including all tested *Staphylococcus*, *Streptococcus* and *Enterococcus* strains. Around this time, Brandl and Knauseder[83] found that pleuromutilin was also active against resistant bacteria such as penicillin- and streptomycin-resistant *staphylococci* and was highly active against *Mycoplasma spp*.

Thousands of pleuromutilin derivatives have been prepared by modification of the C-14 side chain or tricyclic core,[84–86] but only sulfanylacetyl derivatives, most of which contain a basic amine residue on the C-14 extension, have advanced into or beyond Phase I clinical studies. Tiamulin **175** (Denegard®) (Figure 39) was the first antibiotic developed at Sandoz in 1975.[87] It is highly active against many Gram-positive bacteria and is used as a prophylactic and therapeutic treatment for bacterial infections in farm animals.[88] In 1999, Novartis launched valnemulin **176** (Econor®)[89,90] which has broad spectrum activity against Gram-positive pathogens. Valnemulin has superior antimicrobial activity, against many of the same strains, than tiamulin.[91] Although it is primarily used in veterinary medicine, valnemulin has been used in humans to treat life-threatening drug-resistant *Mycoplasma* infections in immune-compromised patients.[92]

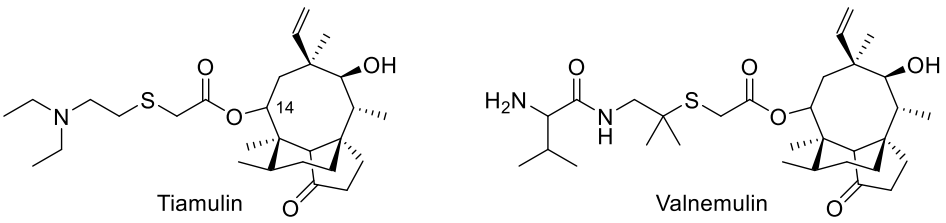


Figure 39. Structures of tiamulin and valnemulin

In 1982, azamulin **177** (Figure 40) intended for human use was synthesised by Berner[93] and disclosed by GlaxoSmithKline. Azamulin was reported to have good oral bioavailability at dosage levels appropriate for clinical use, despite its extensive metabolism by cytochrome P450 oxidation. However, azamulin did not progress beyond a Phase I clinical trial because it was found to be a strong and irreversible inhibitor of CYP3A.[85] It was not until 2007 that the first pleuromutilin, retapamulin **178** (Altargo®) for clinical use was introduced. Retapamulin shows excellent potency against *S. aureus* and *S pyrogenes*.[94] It is used as a topical, short-term treatment for skin and soft tissue infections including impetigo and small infected lacerations, abrasions, or sutured wounds.[95]

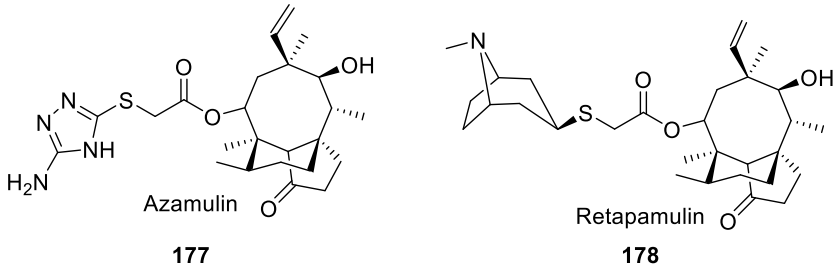


Figure 40. Structures of Azamulin and Retapamulin

Nabriva Therapeutics has extensively investigated C-14 derivatives of (+)-pleuromutilin and identified lefamulin **179** (BC-3781) as potentially a drug suitable for systemic use in humans (Figure 41).[85] Lefamulin **179** has shown promising activity[96] for a number of clinical applications including acquired bacterial pneumonia, acute bacterial skin infections (Phase 2 completed) and sexually transmitted infections (Phase 1 completed), among others. Lefamulin exhibits excellent potency against a broad spectrum of Gram-positive bacteria, especially drug- and multidrug-resistant isolates.[97] Nabriva have also developed BC-7013,[98] a novel topical pleuromutilin, which recently completed Phase 2 clinical trials for the treatment of uncomplicated skin infections.[96] BC-7013 is highly active against Gram-positive bacteria that cause skin and ocular infections and has also demonstrated potent activity against *Chlamydia trachomatis*, the leading cause of blindness in the world, and *Propionibacterium acnes*, the causative agent of acne.[99]

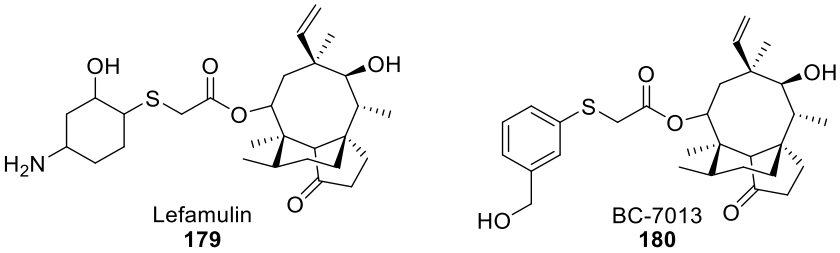
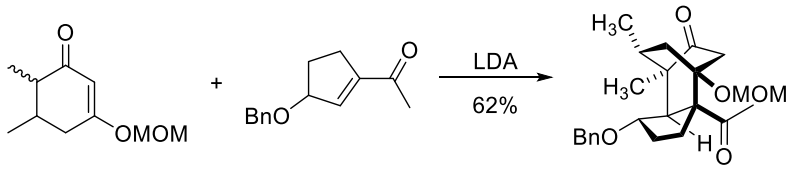


Figure 41. Structures of lefamulin and BC-7013

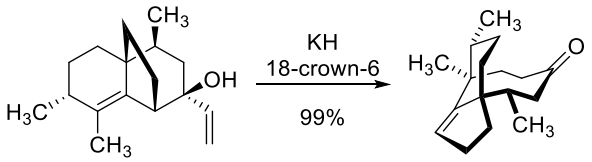
2.1.2 Total syntheses of pleuromutilin

Pleuromutilin has received significant attention from the synthetic community not only because of its bioactivity but also its unusual carbon skeleton bearing three fused rings and eight stereocenters. The first total synthesis of (±)-pleuromutilin was completed by Gibbons.[100] His approach to the tricyclic system was based on a sequential Michael strategy which rapidly assembled the hydrindane core (Scheme 59).



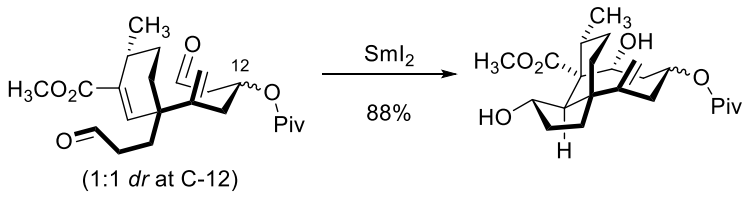
Scheme 59. Key step in the Gibbons synthesis of pleuromutilin[100]

Shortly after, Boeckman[101] reported the second route to the target which utilised an anionic oxy-Cope rearrangement to form the eight-membered ring (Scheme 60).



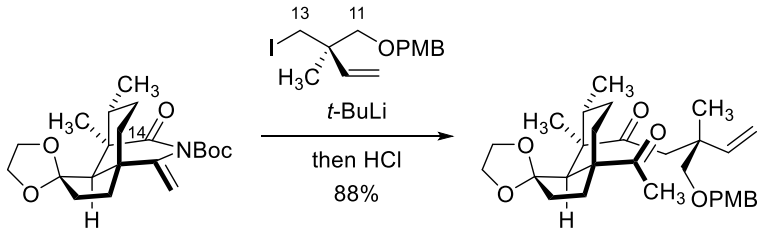
Scheme 60. Key step in the Boeckman synthesis of pleuromutilin[101]

In 2013 Procter and co-workers[102] reported the first enantioselective synthesis of (+)-pleuromutilin. The key step of the synthesis was the SmI_2-mediated cascade cyclisation to form the 5,6,8-trycyclic core, constructing four contiguous stereocentres and two new rings in a single step[84] (Scheme 61).



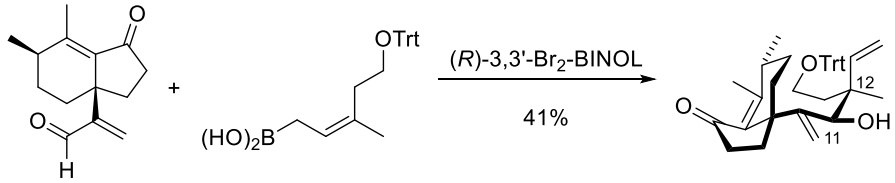
Scheme 61. Key step in the Procter synthesis of (+)-pleuromutilin[102]

In 2017, Herzon and co-workers[103] developed an enantioselective synthetic route that relies on the convergent union of a complex hydridane derivate with a bifunctional C-11-C-13 synthon.



Scheme 62. Key step in the Herzon synthesis of (+)-pleuromutilin[103]

The most recent enantioselective synthesis of (+)-pleuromutilin was reported by Reisman and co-workers[104] which employs an allylborate addition as the key step to establish the C-12 stereocenter leading to (+)-pleuromutilin in 18 steps.



Scheme 63. Key step in the Reisman synthesis of (+)-pleuromutilin[104]

Due to the many steps required for the total synthesis of pleuromutilin, the low yields and the high costs, total synthesis have not been used for large-scale production of the antibiotic. Hence, it appears that despite the efforts of several groups, total synthesis of pleuromutilin does not seem to be a cost-effective alternative to purification of the antibiotic fungal cultures.

2.1.3 Biosynthesis of (+)-pleuromutilin

In the 1960s the first investigations into the biosynthesis of pleuromutilin were undertaken by Birch,[80] who confirmed the structure for pleuromutilin proposed by Arigoni,[79] as well as proving through incorporation of ^{14}C-labelled acetic and mevalonic acids that pleuromutilin was a diterpene. In 1976 Knauseder and Brandl[83] carried out a large-scale fermentation of *C. passeckerianus* with the aim of isolating possible intermediates during the biosynthesis of pleuromutilin. At the end of the fermentation, pleuromutilin **174**, mutilin **181**, 14-*O*-acetyl mutilin **182**, and a series of pleuromutilin esters were isolated from the dried mycelium. It was proposed that mutilin **181** and 14-*O*-acetyl-mutilin **182** could be the products of a secondary pathway that would branch from the main pathway of the antibiotic and would terminate with 14-O-acetyl-mutiln.

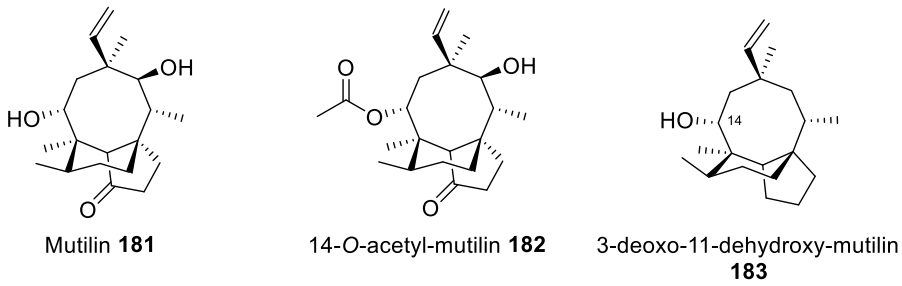
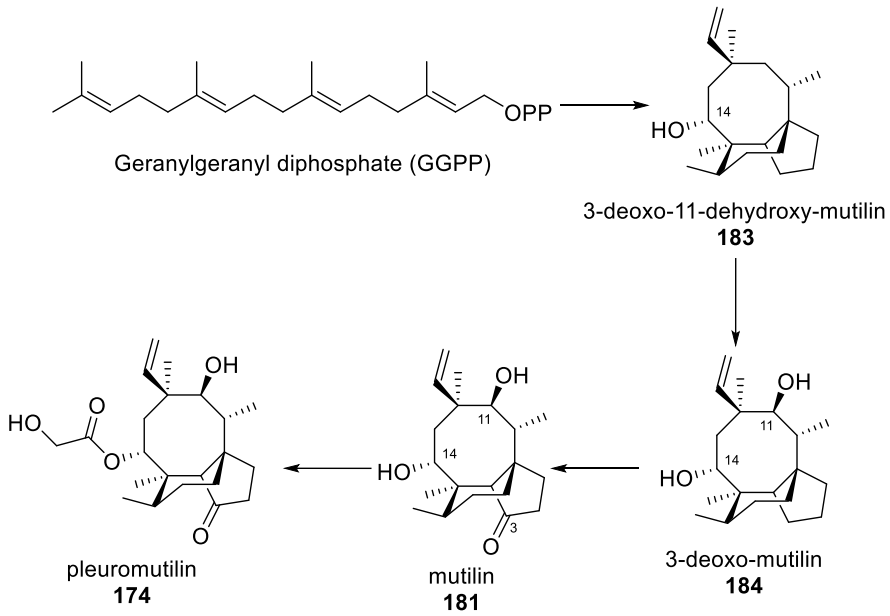


Figure 42. Structures of mutilin **181**, 14-*O*-acetyl-mutilin **182** and 3-deoxo-11-dehydroxy-mutilin **183**

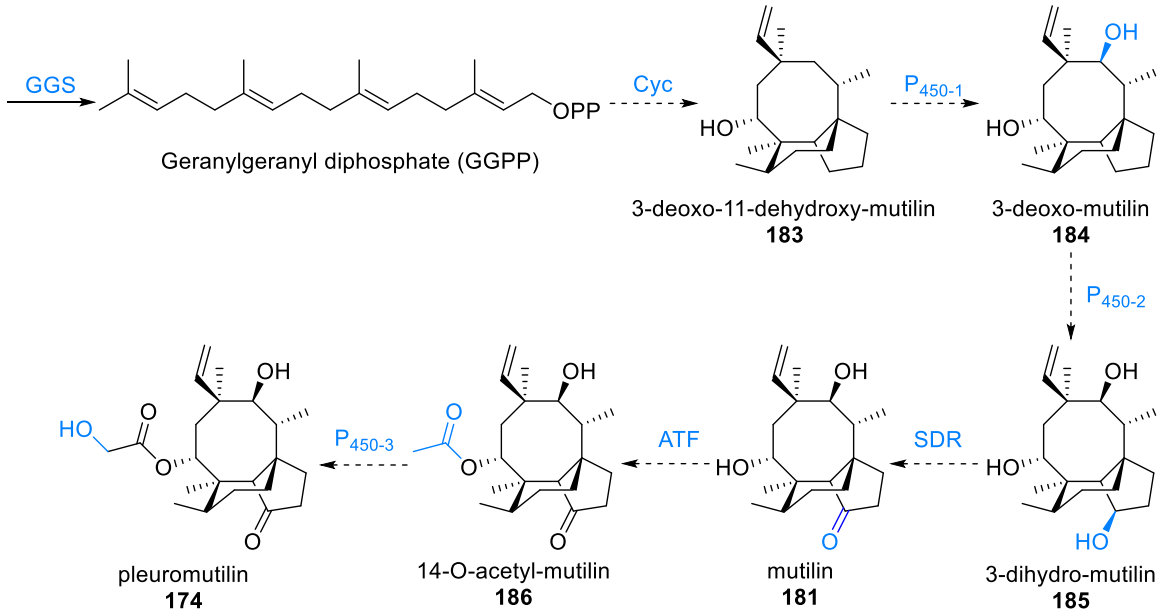
In 1979, Hasler and co-workers[105] reported the isolation of the metabolite 3-deoxo-11-dehydroxy-mutilin **183** from extracts of *P. mutilus* (Figure 42). They proposed that this metabolite would be a precursor of pleuromutilin by feeding a ^{14}C-labelled sample of the compound, prepared from naturally obtained substances, to a culture of the fungus and then isolating ^{14}C-pleuromutilin. They also produced evidence that mutilin **181** and 3-deoxo-mutilin **184** would be two precursors of pleuromutilin, therefore going against the hypothesis of Knauseder and Brandl[83] that mutilin could be the end-product of a secondary pathway.

In 2007, Tsukagoshi and co-workers[106] fed into a culture of the fungus *Clitopilus pseudo-pinsitus,* ^{2}H-labelled samples of mutilin **181**, 3-deoxo-mutilin **184** and 3-deoxo-11-dehydroxy **183** and then isolated ^{2}H-pleuromutilin from the corresponding mycelial cultures, proving as Hasler[105] proposed, their role as biosynthetic intermediates. From these results, the proposed pleuromutilin biosynthetic pathway is shown in Scheme 64.



Scheme 64. Proposed biosynthetic pathway to pleuromutilin[106]

More recently Bailey´s group[107] in the Department of Biological Science at the University of Bristol working in collaboration with our group have conducted further studies on the biosynthesis of pleuromutilin in *C. passeckerianus*. The gene cluster responsible for the biosynthesis of pleuromutilin was identified in this fungus leading to a patent,[108] where the sequence of the putative gene cluster was revealed. Seven genes were proposed to be involved in the production of pleuromutilin. Firstly, there is a specific geranylgeranyl diphosphate synthase gene (*GGS*) responsible for providing geranylgeranyl diphosphate (GGPP) for the biosynthesis of pleuromutilin. Then, there are six other genes adjacent to *GGS* with potential roles in secondary metabolite biosynthesis (Scheme 65). These included a gene encoding a cyclase (*Cyc*) which commonly catalyses the cyclisation of GGPP to give the proposed first cyclic intermediate **183**, as well as genes encoding acetyl transferase (*ATF*), short-chain dehydrogenase/reductase (*SDR*) and three cytochrome P450s (P450-1, P450-2 and P450-3). It was confirmed by Bailey and co-workers[107] by Northern blot analyses and gene silencing experiments that these seven genes were putatively involved in the biosynthesis of the antibiotic.



Scheme 65. Proposed biosynthetic pathway of pleuromutilin in which the seven cloned genes are shown over arrows.

Heterologous expression of the seven genes in the secondary host *Aspergillus oryzae* (*GGS*, *Cyc*, P450-1, P450-2, P450-3, *ATF* and *SDR* from the native produced *C. passeckerianus*) recreated the biosynthesis of the antibiotic and demonstrated that these genes formed the pleuromutilin gene cluster.

2.2 Aim of the Project

To confirm the proposed biosynthetic pathway and determine the function of each individual gene Fabrizio Alberti, a former PhD student in Bailey´s group, performed stepwise heterologous expression of genes from the pleuromutilin cluster in *A. oryzae* and isolated the products. In a collaborative project, my aim was to synthesise three of the putative metabolites **181**, **183** and **184** (Figure 43) to give standards for comparison with the isolated products.[109] This work has been published in *Nature Communications* (Heterologous expression reveals the biosynthesis of the antibiotic pleuromutilin and generates bioactive semi-synthetic derivatives F. Alberti, K. Khairudin, **E. Rodriguez-Venegas**, J. A. Davies, P. M. Hayes, C. L. Willis. A. M. Bailey and G. D. Forster, *Nat Commun.*, **2017**, 8, 1831.)

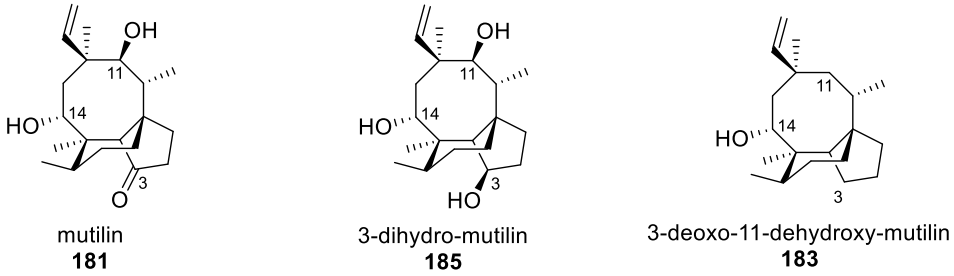


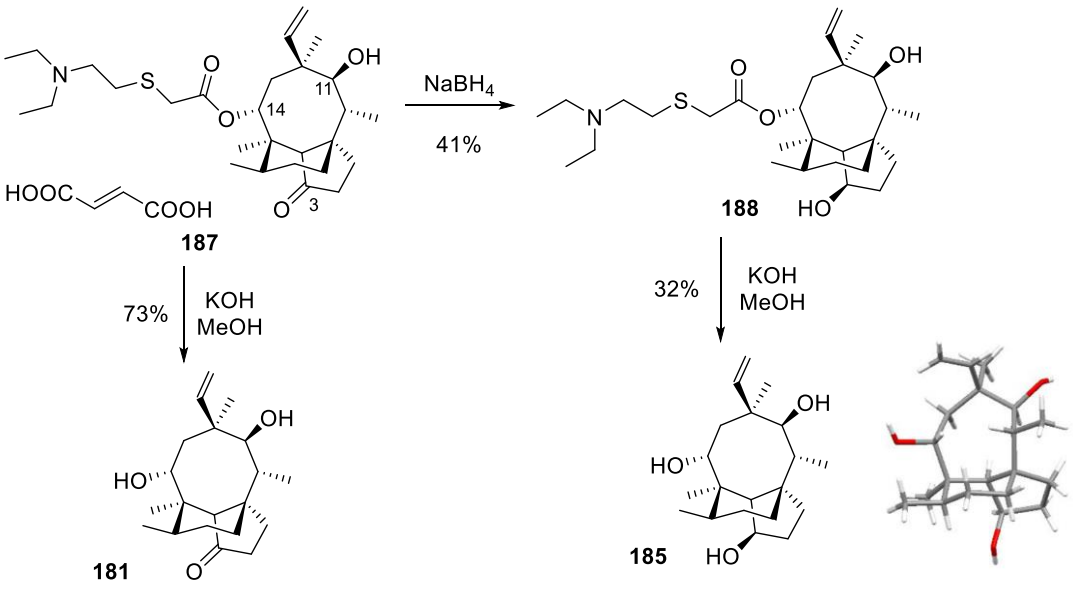
Figure 43. Synthetic targets

2.3 Results and Discussion

Concurrent with my work, Alberti continued to investigate the biosynthetic pathway of pleuromutilin by introduction of the cytochrome *P450-1* gene along with *GGS* and *Cyc* producing 3-deoxo-mutilin **184** into *A. oryzae*. This diol had been previously reported by Hasler[105] and by comparison with their spectral data, confirmed **184** to be the second intermediate in the biosynthetic pathway of pleuromutilin. An *A. oryzae* transformant strain was then constructed harbouring *GGS*, *Cyc*, *P450-1* and *P450-2* from *C. passeckerianus* which gave 3-dihydro-mutilin **185**. This triol was novel and had not been reported in the literature, thus was one of my synthetic targets. Next, Alberti added the cDNA of the *SDR* gene to an *A. oryzae* host that also contained *GGS*, *Cyc, P450-1* and *P450-2* and this system showed the production of mutilin **181** which was first observed by Knauseder and Brandl[83] in *C. passeckerianus* and had been hypothesised to be a precursor of pleuromutilin by both Hasler[105] and Tsukagoshi.[106] Mutilin **181** was also synthesised during my research project as described below.

Pleuromutilin is produced industrially *via* large-scale fermentation of *Clitopilus passeckerianus* however, it is not commercially available for research purposes at a reasonable price. Instead, a far more cost-effective source was tiamulin hydrogen fumarate **187** which is available as Denegard®, a solution containing 12.5% of tiamulin hydrogen fumarate (w/v) in aqueous solution. To begin, a solution of Denegard® was concentrated *in vacuo* with toluene to azeotrope off the water to give tiamulin salt **187** in ~ 99% purity (Scheme 66). Reaction of **186** with potassium hydroxide gave mutilin **181** in 73% yield confirming the structure of the product from an *A. oryzae* transformant strain harbouring *GGS*, *Cyc*, *P450-1* and *P450-2* and *SDR*.

Tiamulin salt **187** was treated with $NaBH_4$ to give diol **188** in 41% yield after purification by column chromatography. Diol **188** was heated to reflux in a solution of 5% potassium hydroxide in methanol to hydrolyse the side chain giving triol **185**. The structure was determined by spectroscopic methods and the configuration of the 3-hydroxy group determined by X-ray crystallography (X-ray by Jonathan Davies, PhD student in the group).



Scheme 66. Synthesis of mutilin **181** and triol **185**

Comparison of the ^{1}H and ^{13}C NMR spectra of natural and synthetic triol **185** (Figure 44 & Figure 45) illustrates the excellent correlation between them, supporting the proposed structure of the secondary metabolite **185** produced by the *A. oryzae* transformant strain harbouring *GGS*, *Cyc*, *P450-1* and *P450-2*.

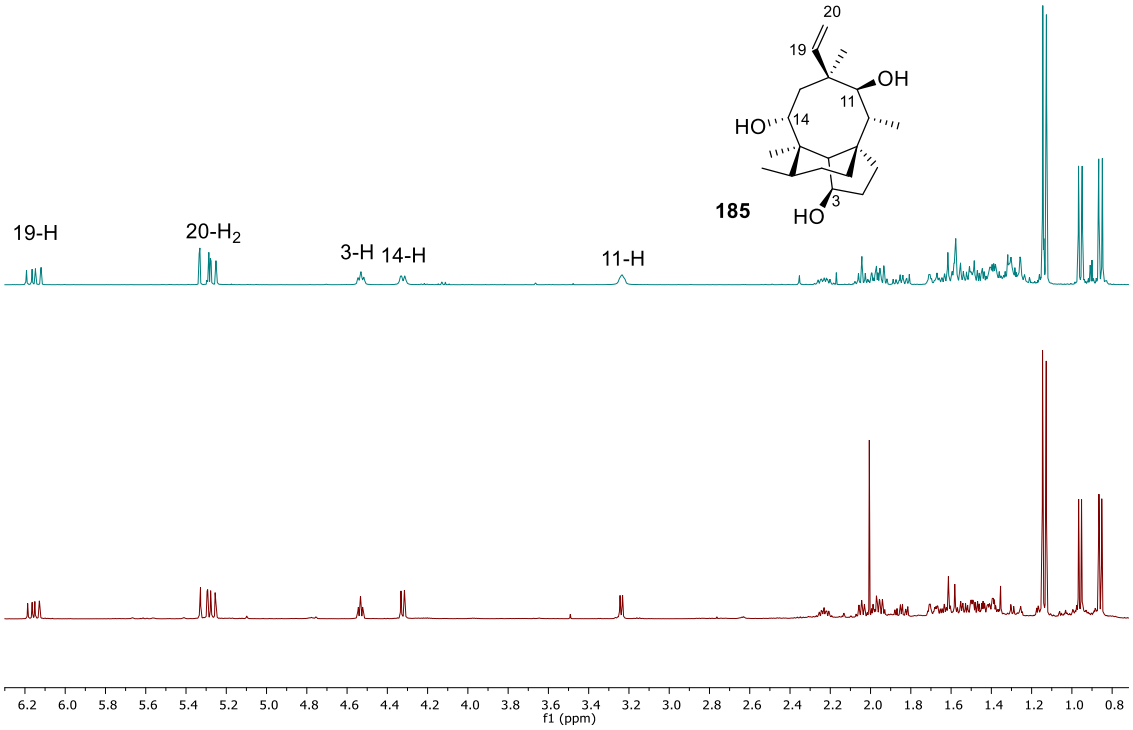


Figure 44. ^{1}H NMR spectra of natural (top) and synthetic triol **184** (bottom)

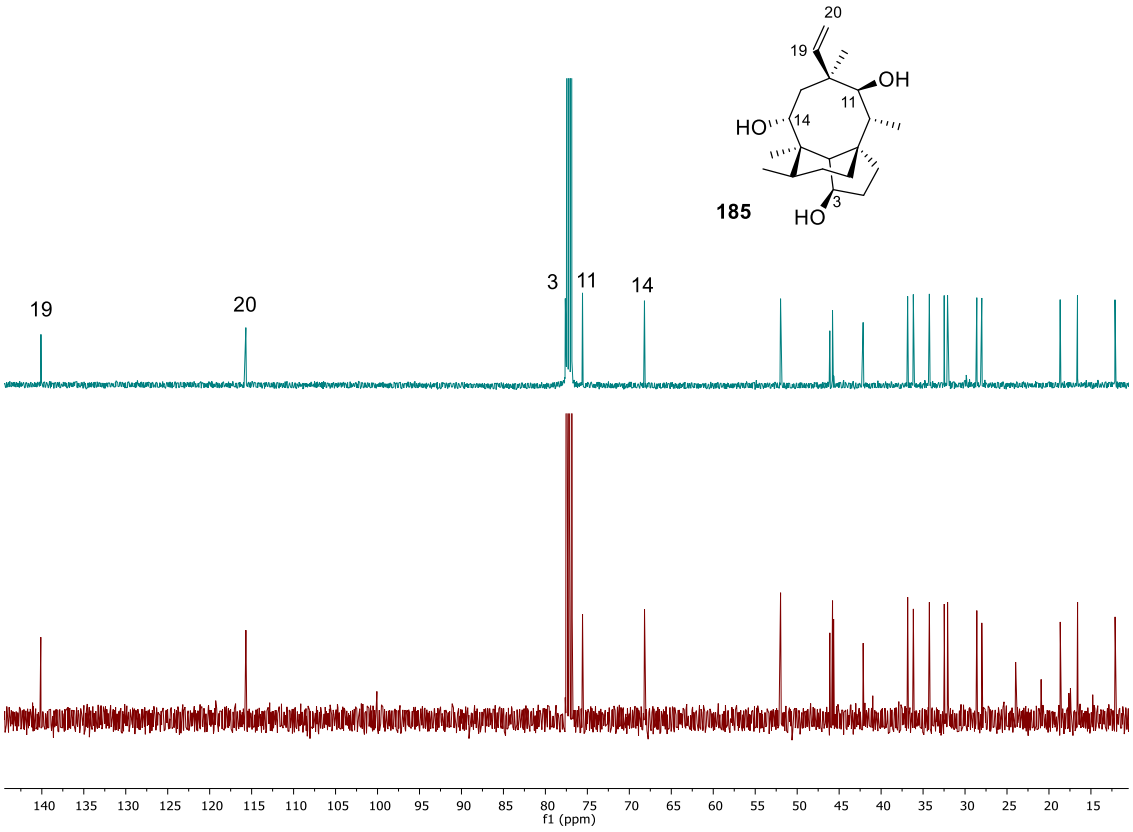
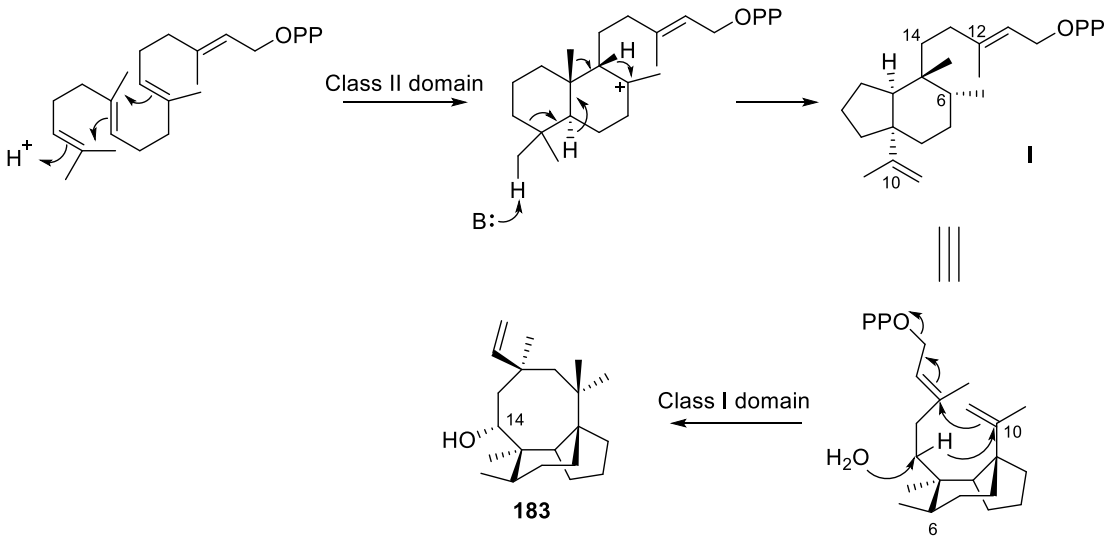


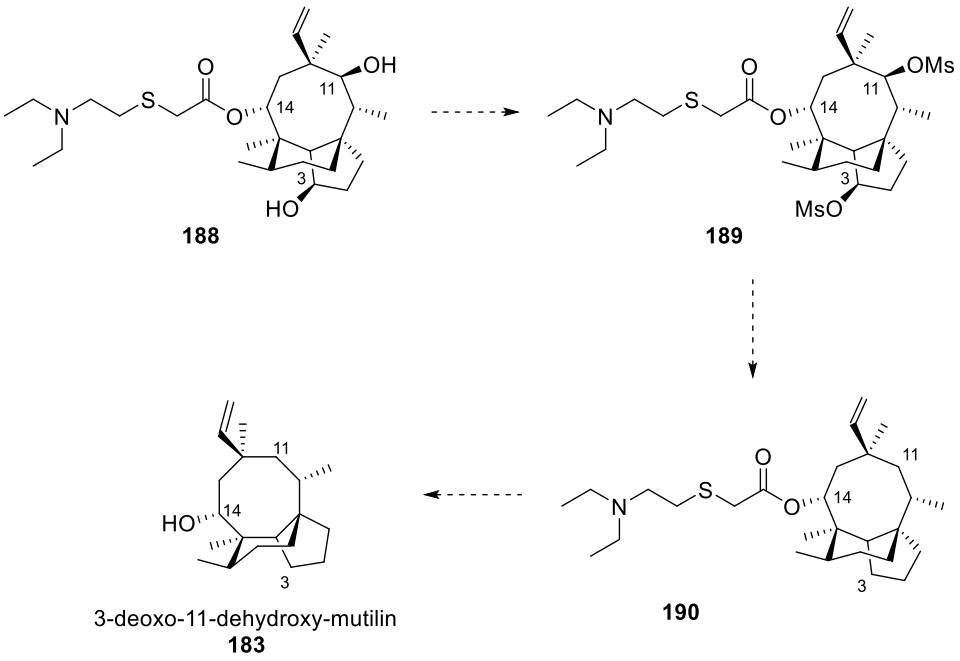
Figure 45. ^{13}C NMR spectra of natural (top) and synthetic triol **184** (bottom)

At this stage, the structures of three of the intermediates **184**, **185** and **181** in the proposed biosynthetic pathway to pleuromutilin (Scheme 65) were now confirmed, and so attention was turned to the first putative cyclic intermediate **183**. This is proposed to be generated from geranylgeranyl pyrophosphate as shown in Scheme 67. Arigoni[79,110] and Birch[80] proposed that the class II terpene synthase domain of *Cyc* promotes ring contraction during the protonation-dependent cyclisation of GGPP giving **I**. The class I terpene synthase domain then catalyses formation of the eight-membered ring through ionisation-dependent dephosphorylation and a shift of 14-H to C-10, then trapping with water introduces the first hydroxy group at C-14 of the tricyclic scaffold.



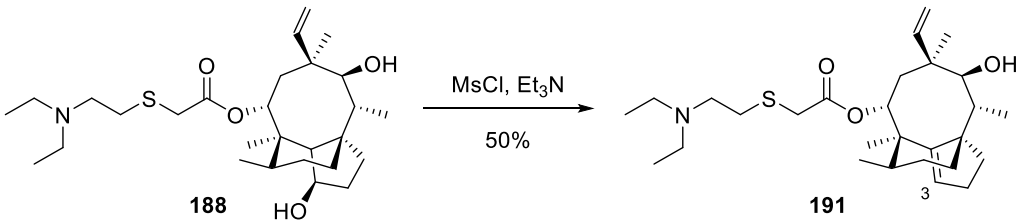
Scheme 67. Outline of cyclisation to the pleuromutilin tricyclic scaffold[79,80,110]

To investigate this step in the biosynthesis of the antibiotic, the cDNA of *GGS* and *Cyc* were co-expressed in *A. oryzae* by Alberti. However, reverse-phase HPLC using a gradient of H_2O containing 0.05% of formic acid and CH_3CN containing 0.045% formic acid failed to detect any new product.[109] It was speculated that the non-polar product was not being eluted from the column. Hence the extract was examined by thin-layer chromatography (TLC) and a new spot was apparent. Preparative TLC was used to purify 14-alcohol **183**, yielding 5 mg from 1 L of culture. To confirm the structure of product **183** a synthetic standard was required, hence 14-alcohol **183** was prepared by partial synthesis diol **188** (Scheme 68). This could be achieved by removing the 3- and 11-alcohols as well as hydrolyse the C-14 side chain to the alcohol.



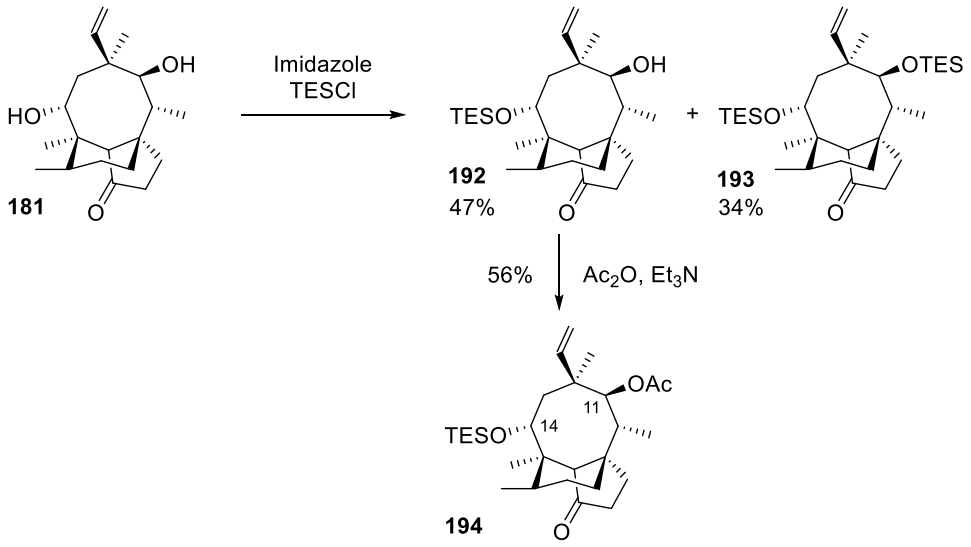
Scheme 68. Proposed synthesis towards alcohol **183**

Diol **188** was treated with MsCl and Et_3N (Scheme 69). Unfortunately, desired mesylate **189** was not observed and alkene **191** was isolated in 50% yield. The trisubstituted alkene was evident from both the ^{13}C NMR (δ 152.4 for C-4 & δ 126.4 for C-3) and ^{1}H-NMR spectra (δ 5.55 for 3-H).



Scheme 69. Reaction of diol **188** with MsCl

Following this disappointing result, a stepwise sequence was investigated. Mutilin **181** was treated with TESCl in the presence of imidazole giving mono- and di-protected silyl ethers **192** and **193** in 47% and 34% yield respectively. To verify that mono-protection had occurred at the required 14-hydroxyl group, acetylation of **192** under standard conditions gave acetate **194** in 56% yield (Scheme 70).



Scheme 70. Synthesis of silyl ethers **192, 193** and acetate **194**

Comparison of the ^{1}H NMR spectra (Figure 46) between **192** and **194** showed the downfield shift of the signal assigned to 11-H to δ4.87 ppm when acetylated in **194**, compared to δ3.34 ppm in alcohol **192**, confirming the TES protection of alcohol at C-14.

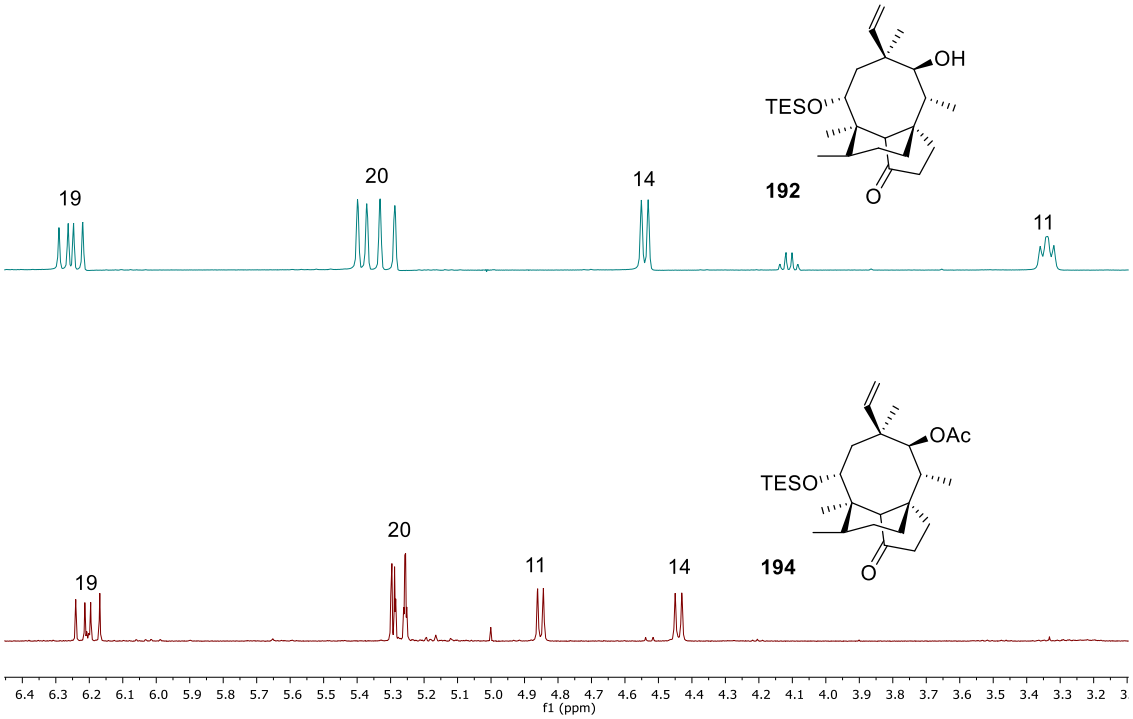
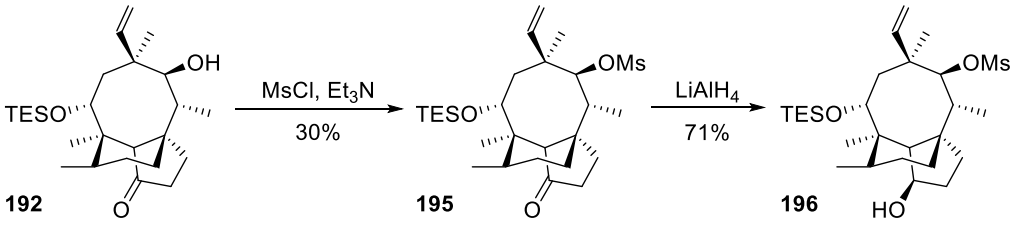


Figure 46. Diagnostic signals of ^{1}H NMR spectra of alcohol **192** and acetate **194**

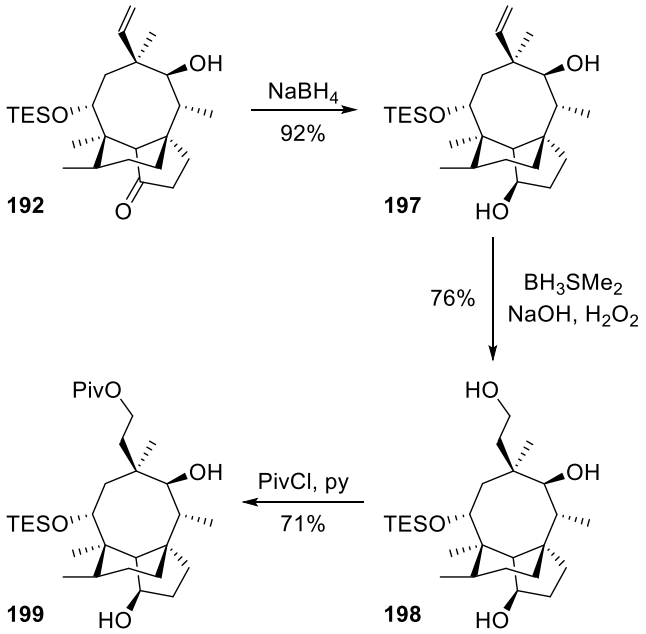
With the protection on the correct hydroxyl group achieved, alcohol **192** was treated with MsCl and Et_3N to give mesylate **195** in only 30% yield along with 15% starting material **192** recovered

(Scheme 71). Reduction of mesylate **195** with $LiAlH_4$ led to reduction of the-ketone as expected but no deoxygenation at C-11 occurred. Further conditions were investigated including $LiAlH_4$ under reflux, $LiBH_4$ and $NaBH_4$/LiCl but each time only alcohol **196** was obtained. Changing the leaving group to a tosylate was investigated by reaction of alcohol **195** with TsCl and pyridine, but the 11-hydroxyl group was too hindered to allow the addition of the tosylate group.



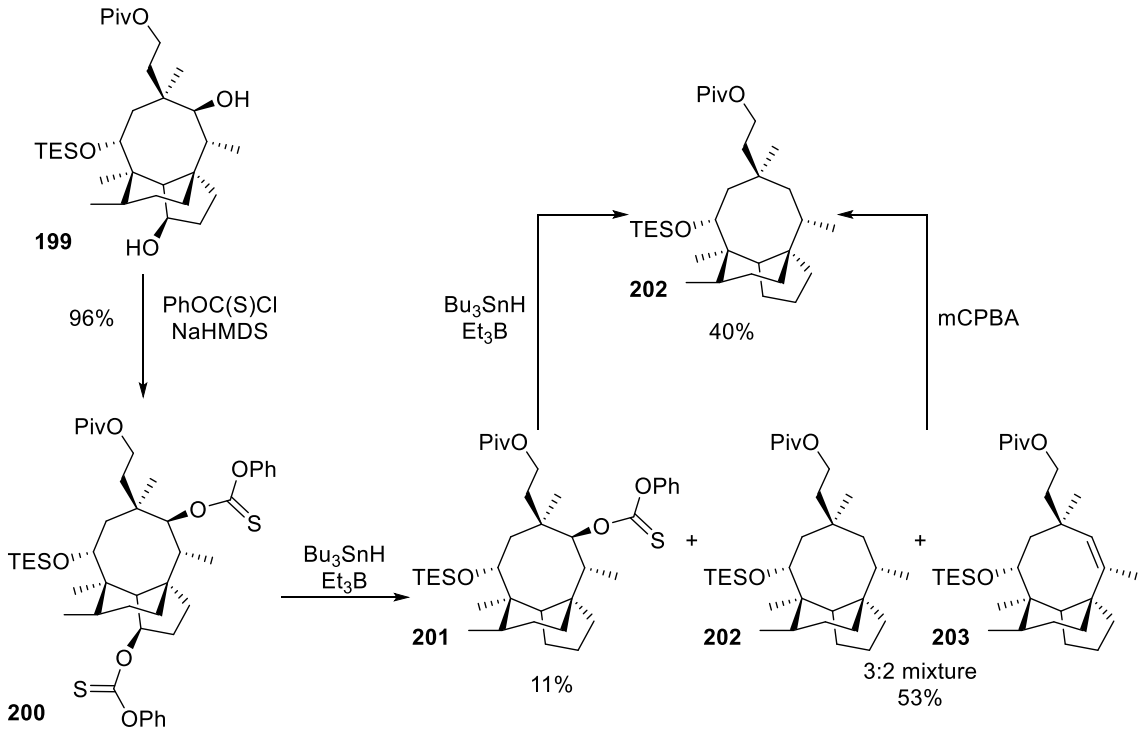
Scheme 71. Synthesis of sulfonate ester **195** and alcohol **196**

Tsukagoshi and co-workers[106] have reported the synthesis of a deuterated analogue of the required alcohol **183** *via* a Barton McCombie deoxygenation reaction. Thus, following this literature approach, ketone **192** was treated with $NaBH_4$ to give diol **197** (Scheme 72). As the Barton McCombie deoxygenation proceeds through a free radical mechanism, the 19,20-alkene required protection. Therefore, mono-protected diol **197** was converted to triol **198** *via* hydroboration-oxidation using borane dimethylsulfide (BMS), NaOH and H_2O_2. Then, the new primary alcohol **198** was protected with addition of pivaloyl chloride to obtain pivalate ester **199** in 71% yield.



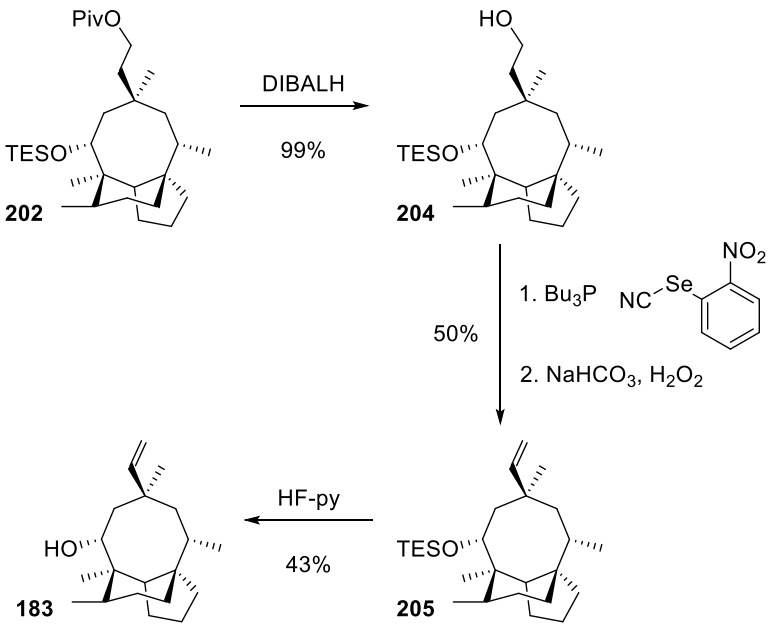
Scheme 72. Synthesis of diol **199**

With the required protecting groups in place, the deoxygenation was investigated. Thus, diol **199** was reacted with phenyl thionochloroformate in the presence of NaHMDS producing thiocarbonyl ester **200** in 96% yield (Scheme 73). Treatment of thiocarbonyl ester **200** with Bu_3SnH and Et_3B produced a 3:2 inseparable mixture of required 3,11-deoxy product **202** and alkene **203** in 53% yield. Furthermore, partially deoxygenated product **201** was isolated in 11% yield which was reduced to **202** using further Bu_3SnH and Et_3B radical conditions. In order to assist with the purification of the required 3,11-deoxy compound **202**, the mixture of **202** and **203** was treated with *m*CPBA to epoxidise the alkene. After purification by column chromatography the desired product **202** was isolated in 35% over the two steps, the epoxide was observed in the ^1H NMR of the crude mixture but not isolated.



Scheme 73. Synthesis of deoxygenated compound **202**

With the desired deoxygenated product **202** in hand, it was necessary to regenerate the 19,20-alkene (Scheme 74). Thus, pivaloyl ester **202** was reduced with DIBALH to give alcohol **204** in quantitative yield. The terminal alkene was reincorporated *via* a Grieco elimination by treatment of alcohol **204** with nitrophenylselenocyanate and tributylphosphine to form a selenide which upon oxidation with H_2O_2 led to elimination to alkene **205** in 50% yield. Finally, silyl ether **205** was deprotected using HF-pyridine to give alcohol **183** in 43% yield.



Scheme 74. Synthesis of target alcohol **183**

Having synthesised alcohol **183**, its ^{1}H and ^{13}C NMR spectra were compared with those of the natural product isolated from the extracts of *A. oryzae* by Alberti (Figure 47 & Figure 48). The excellent correlation between their NMR spectra confirmed the structure of the natural product as being this the first precursor in the biosynthetic pathway of pleuromutilin.

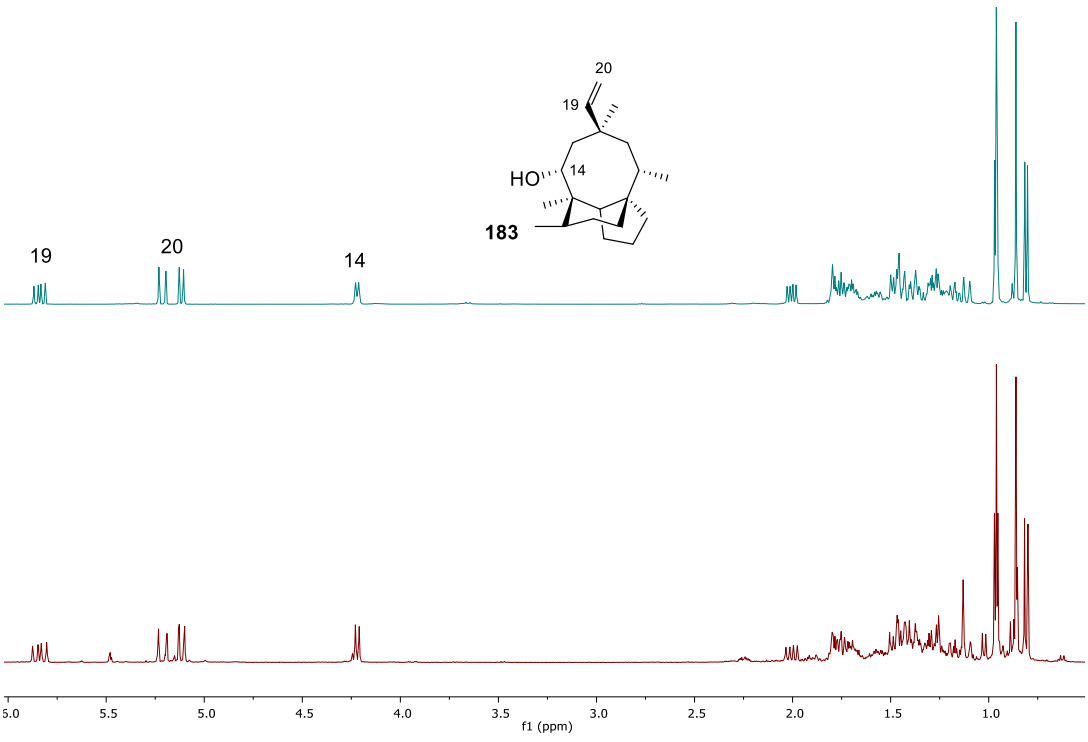


Figure 47. ^{1}H NMR spectra of natural (top) and synthetic product (bottom) **183**

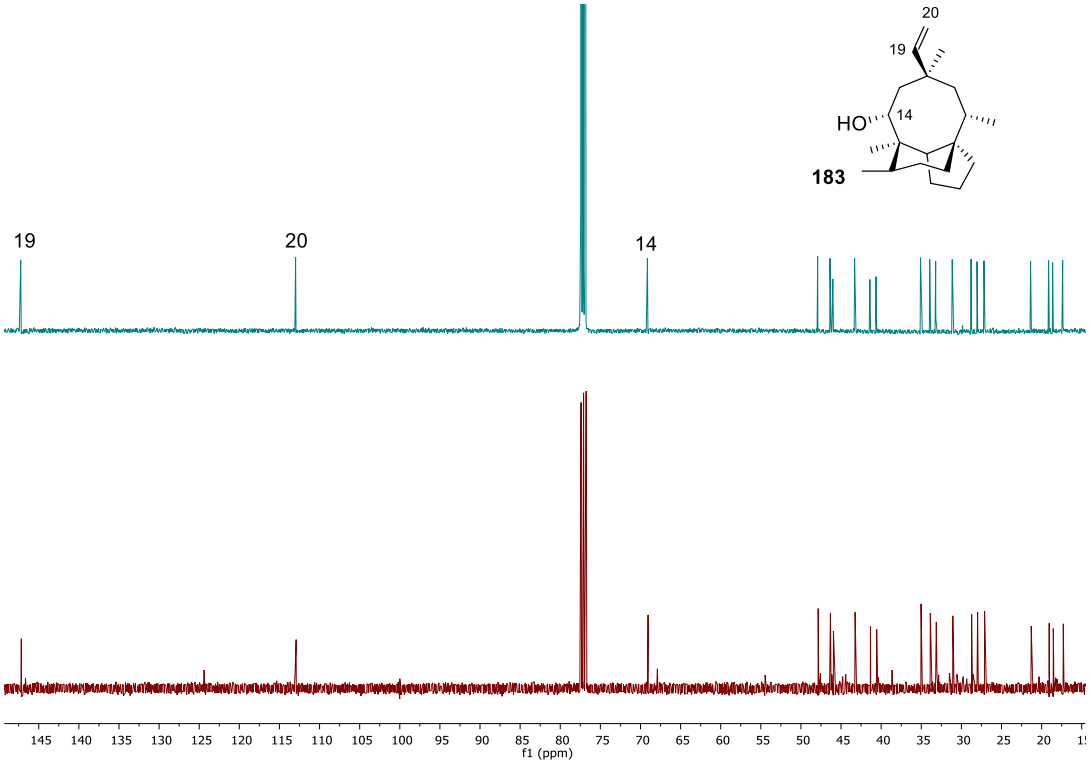
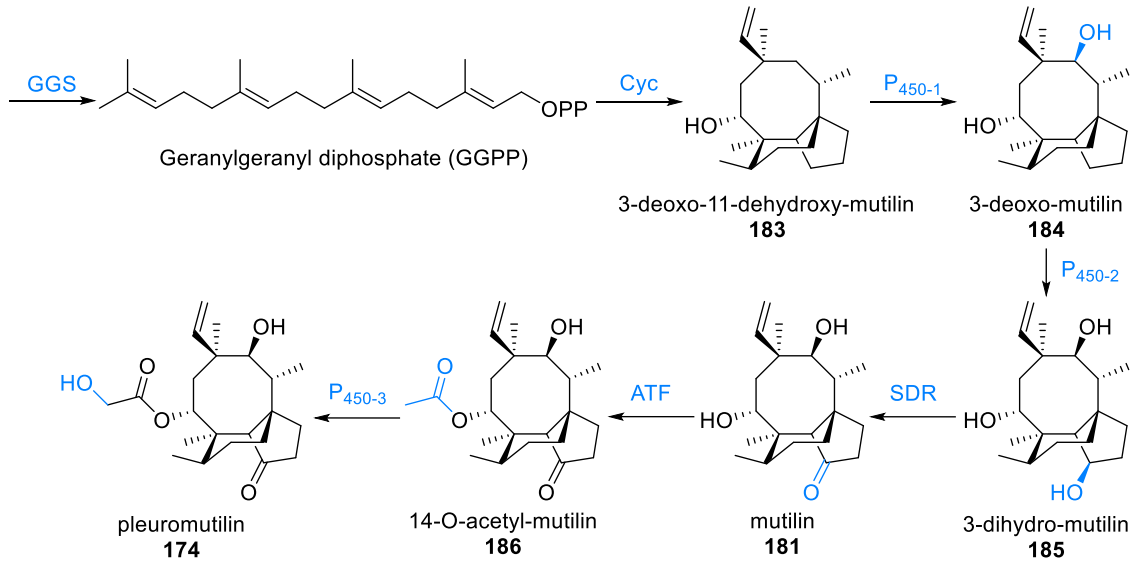


Figure 48. ^{13}C NMR spectra of natural (top) and synthetic product (bottom) **183**

Heterologous expression of the *c*DNA of an acetyl-transferase (*ATF*) gene along with *GGS*, *Cyc*, P450-1, P450-2 and *SDR* in *A. oryzae* produced 14-*O*-acetyl mutilin **186** proving that *ATF* is catalysing esterification of the hydroxyl group from C-14 in mutilin **181**. At this point the *A. oryzae* 6-gene transformant strain producing 14-*O*-acetyl mutilin **186** was only lacking the gene *P450-3* in comparison with the *A. oryzae* 7-gene transformant that produced pleuromutilin **174**. Hence, it can be inferred from this that cytochrome P450-3 catalyses conversion of 14-*O*-acetyl-mutilin **181** to pleuromutilin **174** thus, completing the elucidation of the biosynthetic pathway of pleuromutilin shown in Scheme 75.



Scheme 75. Proposed biosynthetic pathway of pleuromutilin

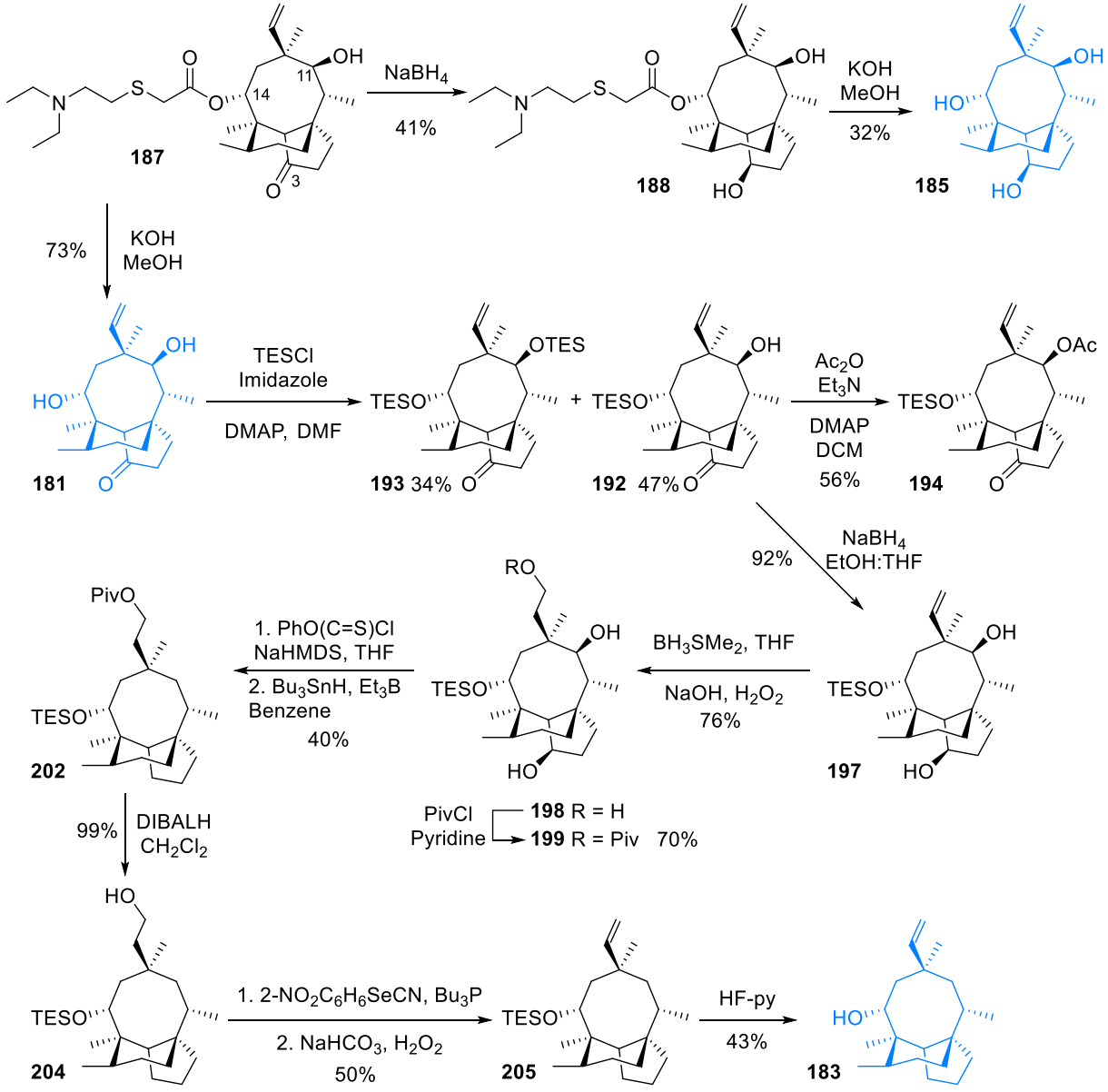
2.4 Conclusions

Three intermediates in the biosynthesis of pleuromutilin were synthesised (Scheme 76). Triol **185** was prepared in two steps from tiamulin **187.** Its ^{1}H and ^{13}C NMR spectra were compared with those of the natural 3-dihydro-mutilin **185** isolated from extracts of the culture of *A. oryzae,* when the transformant contained *GGS*, *Cyc*, P450-1, and P450-2 genes, showing excellent correlation between them.

Mutilin **181**, which was previously reported by Egger[111] and confirmed by Alberti[112] to be a precursor in the biosynthetic pathway of the antibiotic pleuromutilin, was prepared in one steps from tiamulin **187**.

Alcohol **183** was required to confirm the structure of the first cyclic intermediate, 3-deoxo-11-dehydroxy-mutilin **183**, isolated from the extracts of *A. oryzae* when the transformant harboured only *GGS* and *Cyc* genes. A synthetic route to alcohol **183** has been developed. Hydrolysis of tiamulin gave mutilin **181**, which was protected as the 14-monosilyl ether **192**. The regiocontrol in the protection step was confirmed by conversion of alcohol **192** to acetate **194** which showed a characteristic downfield shift of the signal assigned to 11-H in the ^{1}H-NMR spectrum. Following reduction of the 3-ketone to alcohol **197**, the 19,20-alkene was temporarily protected *via* hydroboration and selective esterification of the resultant primary alcohol giving **199**. The 3- and 11-hydroxy groups were removed *via* radical reduction, then pivoyl ester **202** was reduced to alcohol **204**. Following dehydration then deprotection of the silyl ether **205**, the

target alcohol **183** was isolated. The ^{1}H and ^{13}C NMR spectra of the synthetic material and product isolated from extract of *A. oryzae* with the *GGS* and *Cyc* genes were compared showing excellent correlation between them, thus confirming the structure of the natural product.



Scheme 76. Synthesis of triol **185**, mutilin **181** and alcohol **183**

3. Experimental

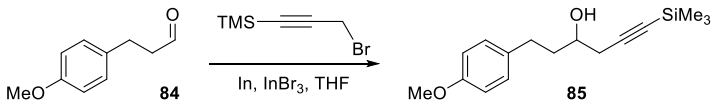
3.1 General experimental

All reagents were sourced from commercial suppliers and were used without further purification. Where anhydrous conditions were necessary, standard Schlenk syringe-septa techniques were used with flame dried glassware under positive pressure of nitrogen. THF, Et_2O, hexane and CH_2Cl_2 were dried by passing through a modified Grubbs system of alumina columns, manufactured by Anhydrous Engineering. All stated temperatures below ambient are the temperatures of the cooling baths, unless otherwise stated. Flash column chromatography was performed using silica gel 60 (Fisher Scientific or Aldrich) and a suitable eluent. TLC was performed with aluminium backed silica TLC plates (Merck-Kieselgel 60 F254) with suitable solvent system and was visualised using UV fluorescence (254 & 366 nm) and/or developed with potassium permanganate.

Infra-red spectra were recorded on a Perkin Elmer Spectrum 100 FTIR with an ATR accessory and frequencies are reported in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded using, Joel ECS 400 MHz, Varian 400-MR (400 MHz), Bruker Advance III HD 500 Cryo (500 MHz) spectrometers at ambient temperature. Chemical shifts (δ) are quoted in parts per million (ppm) and coupling constants (*J*) are in Hertz (Hz). Residual solvent peaks were used as the internal reference for proton and carbon chemical shifts. HRMS ESI were performed on either a Bruker Daltonics Apex 4, 7 Telsa FTICR or microTOF II. Samples were submitted in MeOH or CH_2Cl_2. Optical rotation ([α]TD) was measured on a Bellingham and Stanley Ltd. ADP220 polarimeter and is quoted in $(°ml)(g\ dm)^{-1}$. All HPLC purifications and analyses were performed on an Agilent 1260 Infinity II LC System using either a Waters SunFire Prep silica column or a Regis Technologies (*R*,*R*)-Whelk 01.

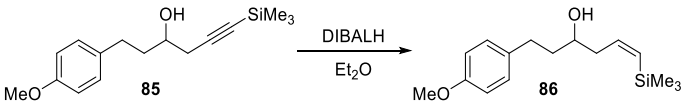
3.2 Experimental procedures chapter 1

1-(4-Methoxyphenyl)-6-trimethylsilylhex-5-yn-3-ol 85



3-(Trimethylsilyl)propargyl bromide (1.09 g, 5.71 mmol) was added to a suspension of In powder (0.66 g, 5.71 mmol) and $InBr_3$ (0.16 g, 0.46 mmol) in THF (5.7 mL) under nitrogen. After stirring for 10 min aldehyde **84** (0.75 g, 4.57 mmol) was added. The mixture was heated to reflux for 20 h, then, 1M HCl solution (10 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The residue was purified by column chromatography using 5-20% EtOAc in petroleum ether 40-60 °C to give alcohol **85** as a colourless oil (0.82 g, 65%).ν_{max} (neat)/cm^{-1}: 3855, 3672, 3473, 2933, 1601, 1510; δ_H (400 MHz, $CDCl_3$) 7.12 (2H, d, *J* 9, Ar), 6.83 (2H, d, *J* 9, Ar), 3.79 (3H, s, OCH_3), 3.74 (1H, m, 3-H), 2.78 – 2.60 (2H, m, 1-H_2), 2.47 (1H, dd, *J* 17, 5, 4-*H*H), 2.37 (1H, dd, *J* 17, 7, 4-H*H*), 1.82 (2H, m, 2-H_2), 0.16 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 157.9, 133.8, 129.4, 113.9, 103.1 (C-5), 87.9 (C-6), 69.1 (C-3), 55.3 (OCH_3), 38.1 (C-2), 31.0 (C-1), 29.0 (C-4), 0.15 ($Si(CH_3)_3$); Found (ESI) 299.1443 [MNa^+] ($C_{16}H_{24}O_2SiNa$ requires 299.1438).

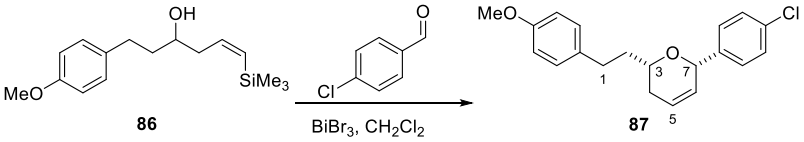
(*Z*)-1-(4-methoxyphenyl)-6-trimethylsilylhex-5-en-3-ol 86



DIBALH (1 M, 8.5 mL, 8.46 mmol) was added dropwise to a solution of alcohol **85** (0.90 g, 3.25 mmol) in anhydrous Et_2O (5 mL) under nitrogen at 0 °C. The reaction mixture was stirred at room temperature for 16 h, then MeOH (50 mL) and Rochelle's salt solution (50 mL) were added and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with water (50 mL) and a saturated solution of brine (50 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The residue was purified by column chromatography using 5-10% EtOAc in petroleum ether 40-60 °C to give alcohol **86** as a colourless oil (0.47 g, 52%). ν_{max} (neat)/cm^{-1}: 3668, 2976, 2836, 1733, 1609, 1511; δ_H (400 MHz, $CDCl_3$) 7.13 (2H, d, *J* 9, Ar), 6.83 (2H, d, *J* 9, Ar), 6.31 (1H, m, 5-H), 5.69 (1H, d, *J* 14, 6-H), 3.79 (3H, s, OCH_3), 3.68 (1H, m, 3-H), 2.76 (1H, m, 1-*H*H), 2.65 (1H, m, 1-H*H*), 2.35 – 2.29 (2H, m, 4-H_2), 1.79 – 1.74 (2H, m, 2-H_2), 0.13 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 157.0, 144.1 (C-5), 134.1,

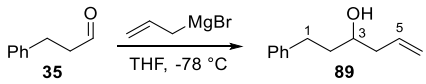
133.2 (C-6), 129.4, 113.9, 70.6 (C-3), 55.3 (OCH_3), 41.4 (C-4), 38.8 (C-2), 31.2 (C-1), 0.34 ($Si(CH_3)_3$); Found (ESI) 301.1585 [MNa^+] ($C_{16}H_{26}O_2SiNa$ requires 301.1594).

7-(*p*-Chlorophenyl)-3-(*p*-methoxyphenethyl)-3,4-dihydro-2H-pyran 87



p-Chlorobenzaldehyde (0.33 g, 2.37 mmol) and a solution of alcohol **86** (0.33 g, 1.185 mmol) in anhydrous CH_2Cl_2 (1.8 mL) were added to a solution of $BiBr_3$ (0.027 g, 0.06 mmol) in CH_2Cl_2 (10 mL) under nitrogen. After stirring for 15 h the reaction mixture was filtered through silica gel and the solvent was evaporated *in vacuo*. The residue was treated with $NaBH_4$ (0.09 g, 2.37 mmol) in MeOH (10 mL) for 0.5 h to reduce any residual aldehyde. Water (10 mL) was added and the solution was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by column chromatography using 2% Et_2O in petroleum ether 40-60 °C to give dihydropyran **87** as a colourless oil (0.225 g, 58%). ν_{max} (neat)/cm^{-1}: 3434, 2932, 1689, 1611, 1590, 1511; δ_H (400 MHz, $CDCl_3$) 7.33 (4H, s, Ar), 7.12 (2H, d, *J* 9, Ar), 6.83 (2H, *J* 9, Ar), 5.91 (1H, ddt, *J* 10, 6, 2, 5-H), 5.70 (1H, ddt, *J* 10, 3, 1, 6-H), 5.11 (1H, m, 7-H), 3.79 (3H, s, OCH_3), 3.69 (1H, m, 3-H), 2.79 – 2.64 (2H, m, 1-H_2), 2.13 (1H, m, 4-*H*H), 2.05 – 1.89 (2H, m, 4-H*H*, 2-*H*H), 1.79 (1H, m, 2-H*H*); δ_C (100 MHz, $CDCl_3$) 157.8, 140.4, 134.2, 133.5, 129.8 (C-6), 129.4, 128.7, 128.6, 125.3 (C-5), 113.8, 76.9 (C-7), 73.4 (C-3), 55.3 (OCH_3), 37.7 (C-2), 30.9 (C-4), 30.7 (C-1). Found (ESI) 351.1128 [MNa^+] ($C_{20}H_{21}O_2ClNa$ requires 351.1122).

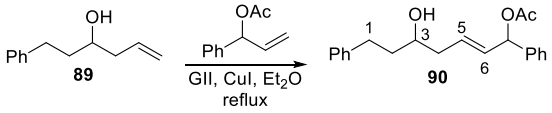
1-Phenylhex-5-en-3-ol 89



Allyl magnesium chloride (28.5 mL, 0.57 mol) was added dropwise to a solution of hydrocinnamaldehyde **35** (5.0 mL, 0.38 mol) in anhydrous THF (126 mL), at −78 °C and stirred for 2.5 h. Semi-saturated solution of NH_4Cl (100 mL) was added and aqueous layer extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The residue was purified by column chromatography using 20% EtOAc in petroleum ether 40-60 °C as eluent to give alcohol **89** as a colourless oil (6.4 g, 95%). δ_H (400 MHz, $CDCl_3$) 7.31 – 7.26 (2H, m, Ar), 7.22 – 7.17 (3H, m, Ar), 5.83 (1H, m, 5-H), 5.17 (1H, m, 6-*H*H), 5.13 (1H, m, 6-H*H*), 3.68 (1H, tt, *J* 7, 4, 3-H), 2.82 (1H, m, 1-*H*H), 2.70 (1H, m, 1-H*H*), 2.33

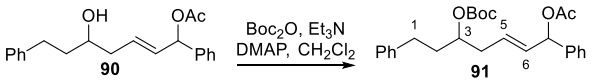
(1H, m, 4-*H*H), 2.19 (1H, m, 4-H*H*), 1.79 (2H, m, 2-H_2), 1.67 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 142.1, 134.7 (C-5), 128.5, 128.5, 125.9, 118.4 (C-6), 70.0 (C-3), 42.1 (C-4) 38.5 (C-2), 32.1 (C-1). Spectroscopic data in accord with the literature.[113]

(E)-7-Acetoxy-1,7-diphenylhept-5-en-3-ol 90



A solution of alcohol **89** (0.25 g, 1.42 mmol) and 1-phenylallyl acetate (0.44 g, 2.48 mmol) in anhydrous Et_2O (14 mL) was degassed with N_2 for 10 min. Then Grubbs catalyst 2nd generation (GII) (0.03 g, 0.035 mmol) and CuI (8.0 mg, 0.042 mmol) were added and the mixture was heated with stirring to reflux. After 2 h, the solvent was evaporated *in vacuo*. The residue was purified by column chromatography using 20% EtOAc in petroleum ether 40-60 °C as eluent to give alcohol **90** as a 1:1 mixture of diastereomers as a colourless oil (0.452 g, 95%). Data given for the mixture ν_{max} (neat)/cm^{-1}: 3025, 2922, 1737, 1494, 1452; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.27 (7H, m, Ar), 7.20 – 7.17 (3H, m, Ar), 6.22 (1H, m, 7-H), 5.76 (2H, m, 5-H, 6-H), 3.68 (1H, m, 3-H), 2.79 (1H, m, 1-*H*H), 2.67 (1H, m, 1-H*H*), 2.31 (1H, m, 4-*H*H), 2.20 (1H, m, 4-H*H*), 2.09 & 2.05 (3H, s, $COCH_3$), 1.76 (2H, m, 2-H_2). δ_C (100 MHz, $CDCl_3$) 170.2 & 170.1 ($COCH_3$), 142.0, 139.5, 139.4, 132.1 & 132.0 (C-5), 130.1 & 129.9 (C6), 128.7, 128.5, 128.5, 128.2, 126.9, 125.9, 76.3 & 76.1 (C-7), 70.2 & 70.0 (C-3), 40.6 & 40.5 (C-4), 38.5 (C-2), 32.0 (C-1), 21.4 ($COCH_3$).; Found (ESI) 347.1605 [MNa^+] ($C_{21}H_{24}O_3Na$ requires 347.1617).

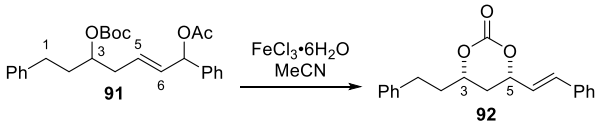
(*E*)-7-Acetoxy-3-*tert*-butoxycarbonyloxy-1,7-diphenylhept-5-ene 91



Et_3N (0.124 mL, 0.89 mmol), DMAP (0.016 g, 0.137 mmol) and Boc_2O (0.60 g, 2.74 mmol) were added to a solution of alcohol **90** (0.22 g, 0.68 mmol) in anhydrous CH_2Cl_2 (6.8 mL). The reaction mixture was stirred for 3.5 h, then the solvent was evaporated *in vacuo*. The residue was purified by column chromatography using 10% EtOAc in petroleum ether 40-60 °C as eluent to give a 1:1 mixture of diastereomers of acetate **91** as a colourless oil (0.29 g, 99%). Data given for the mixture. ν_{max} (neat)/cm^{-1}: 2930, 1734, 1455, 1368; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.25 (7H, m, Ar), 7.20 – 7.13 (3H, m, Ar), 6.23 (1H, m, 7-H), 5.73 (2H, m, 5-H, 6-H), 4.73 (1H, m, 3-H), 2.74 – 2.57 (2H, m, 1-H_2), 2.40 (2H, m, 4-H_2), 2.09 & 2.08 (3H, s, $COCH_3$), 1.86 (2H, m, 2-H_2), 1.49 & 1.47 (9H, s, $OC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 170.0 ($COCH_3$), 153.3 (O(CO)O), 141.4, 139.4, 131.8 (C-5), 128.7

(C-6), 128.6, 128.5, 128.4, 128.1, 127.1, 127.0, 126.0, 82.0 ($OC(CH_3)_3$), 75.9 (C-7), 75.8 (C-3), 37.2 (C-4), 35.6 (C-2), 31.6 (C-1), 27.9 ($OC(CH_3)_3$), 21.4 ($COCH_3$); Found (ESI) 447.2138 [MNa^+] ($C_{26}H_{32}O_5Na$ requires 447.2142).

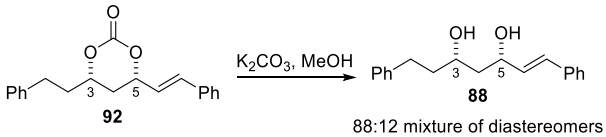
(*E*)-4-Phenethyl-6-styryl-1,3-dioxan-2-one 92



2:1 mixture of diastereomers

$FeCl_3 \cdot 6H_2O$ (2.0 mg, 0.012 mmol) was added to a solution of acetate **91** (0.05 g, 0.12 mmol) in MeCN (1.12 mL) under nitrogen. The reaction mixture was stirred for 5.5 h, then the solvent was evaporated *in vacuo*. The residue was purified by column chromatography using 30% petroleum ether 40-60 °C in EtOAc to give carbonate **92** as a mixture of diastereomers 2.5:1 as a colourless oil (0.21 g, 58%). Data given for the mixture. ν_{max} (neat)/cm^{-1}: 3026, 2923, 1737, 1378; δ_H (400 MHz, $CDCl_3$) 7.41 – 7.17 (10H, m, Ar), 6.71 (0.73H, d, *J* 16, 7-H), 6.69 (0.27H, d, *J* 16, 7-H), 6.16 (0.73H, dd, *J* 16, 7, 6-H), 6.15 (0.27H, dd, *J* 16, 7, 6-H), 5.22 (0.27, q, *J* 5, 5-H), 5.03 (0.73H, dddd, *J* 11, 7, 3, 1, 5-H), 4.55 (0.27H, spt, *J* 5, 3-H), 4.47 (0.73H, m, 3-H), 2.94 – 2.70 (2H, m, 1-H_2), 2.20 – 2.04 (2.27H, m, 4-*H*H, 2-*H*H, 4-H_2), 2.01 – 1.81 (1.73H, m, 4-H*H*, 2-H*H*); δ_C (100 MHz, $CDCl_3$) 150.0 (CO), 140.4, 135.5, 133.7 & 113.5 (C-7), 128.8, 128.7, 128.6, 128.5, 126.9, 126.8, 126.4, 125.1 & 125.0 (C-6), 79.0 & 76.6 (C-5), 77.6 & 75.3 (C-3), 37.0 & 36.7 (C-6), 33.8 & 31.8 (C-4), 31.0 & 30.7 (C-7).

(*E*)-1,7-Diphenylhept-1-ene-3,5-diol 88

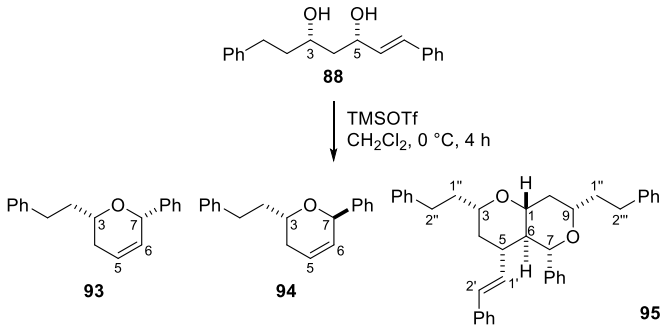


88:12 mixture of diastereomers

A solution of carbonate **92** (0.02 g, 0.065 mmol) in MeOH (1.3 mL) was treated with K_2CO_3 (0.06 g, 0.45 mmol). After stirring the mixture for 1.5 h, EtOAc (2 mL) and a saturated solution of NH_4Cl (2 mL) were added. The mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo* to give diol **88** as a colourless oil as an 88:12 mixture of diastereomers (0.013 g, 73%). Data for the major diastereomer. δ_H (400 MHz, $CDCl_3$) 7.39 – 7.17 (10H, m, Ar), 6.60 (1H, d, *J* 16, 7-H), 6.23 (1H, dd, *J* 16, 7, 6-H), 4.56 (1H, m, 5-H), 3.97 (1H, m, 3-H), 2.84 – 2.65 (2H, m, 1-H_2), 1.90 – 1.79 (2H, m, 2-H_2), 1.78 – 1.74 (2H, m, 4-H_2); δ_C (100 MHz, $CDCl_3$) 142.2, 136.6, 131.9 (C-6), 130.3 (C-7), 128.7, 128.6, 128.5, 127.9,

126.6, 126.0, 73.9 (C-5), 71.8 (C-3), 43.5 (C-4), 39.8 (C-2), 31.9 (C-1). Spectroscopic data in accord with the literature.[114]

Treatment of racemic diol 88 with TMSOTf



Starting diol **88** (0.25 mg, 0.88 mmol) was dissolved in CH_2Cl_2 (9 mL) under nitrogen and the solution was cooled to 0 °C. TMSOTf (8 µL, 0.045 mmol) was added and the mixture was stirred at this temperature for 4.5 h. Water (8 mL) was added and the two phases separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The crude product was purified by column chromatography. Elution with 1% EtOAc in petroleum ether 40-60 °C gave *syn*-dihydropyran **93** (4.6 mg, 2% yield) and *anti*-dihydropyran **94** (34 mg, 15 % yield), elution with 5% EtOAc in petroleum ether 40-60 °C gave blepharocalyxin analogue **95** (26 mg, 11% yield) and finally using 20% EtOAc in petroleum ether 40-60 °C a further mixture of dimeric diarylheptanoids (63 mg, 27% yield) was obtained.

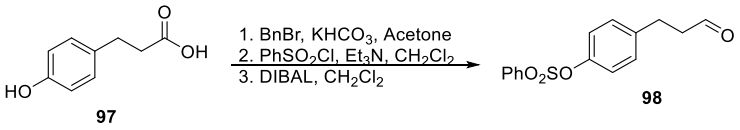
(±)-*Syn*-3-phenethyl-7-phenyl-3,4-dihydro-2H-pyran 93. A colourless oil. ν_{max} (neat)/cm^{-1} 3058, 2931, 2931, 1718, 1689; δ_H (400 MHz, $CDCl_3$) 7.44 – 7.18 (10H, m, Ar), 5.92 (1H, m, 5-H), 5.79 (1H, m, 6-H), 5.17 (1H, m, 7-H), 3.74 (1H, m, 3-H), 2.89 – 2.74 (2H, m, 1-H_2), 2.18 (1H, m, 4-*H*H), 2.08 – 1.97 (2H, m, 4-H*H*, 2-H*H*), 1.85 (1H, m, 2-H*H*); δ_C (100 MHz, $CDCl_3$) 142.3, 141.9, 130.3 (C-6), 128.7, 128.6, 128.4, 127.8, 127.6, 125.8, 124.9 (C-5), 77.7 (C-7), 73.4 (C-3), 37.6 (C-2), 31.7 (C-4), 31.0 (C-1). Found (ESI) 287.1419 [MNa^+] ($C_{19}H_{20}ONa$ requires 287.1406).

(±)-*Anti*-3-phenethyl-7-phenyl-3,4-dihydro-2H-pyran 94. A colourless oil. ν_{max} (neat)/cm^{-1} 3025, 2917, 2857, 1690, 1598, δ_H (400 MHz, $CDCl_3$) 7.46 – 7.34 (5H, m, Ar), 7.18 – 7.10 (3H, m, Ar), 6.93 – 6.90 (2H, m, Ar), 6.09 – 6.00 (2H, m, 5-H, 6-H), 5.32 (1H, s, 7-H), 3.54 (1H, m, 3-H), 2.74 (1H, m, 1-*H*H), 2.52 (1H, m, 1-H*H*), 2.14 – 1.98 (2H, m, 4-H_2), 1.89 (1H, m, 2-*H*H), 1.69 (1H, m, 2-H*H*); δ_C (100 MHz, $CDCl_3$) 142.2, 141.2, 128.6, 128.5, 128.4, 128.3, 127.8, 127.5 (C-6), 126.1

(C-5), 125.6, 74.2 (C-7), 66.4 (C-3), 37.6 (C-2), 31.7 (C-4), 31.2 (C-1). Found (ESI) 287.1407 [MNa^+] ($C_{19}H_{20}ONa$ requires 287.1406). Spectroscopic data in accord with the literature.[115]

(±)-*Trans*-3,9-phenylethyl-7-phenyl-5((*E*)-phenethenyl)-2,8-dioxabicyclo[4.4.0]decane 95. A colourless oil. ν_{max} (neat)/cm^{-1} 3025, 2919, 2854, 1687, 1601; δ_H (400 MHz, $CDCl_3$) 7.50 – 7.06 (17H, m, Ar), 6.99 (1H, m, Ar), 6.73 (2H, m, Ar), 5.82 (1H, d, *J* 16, 2'-H), 5.14 (1H, dd, *J* 16, 9, 1'-H), 4.02 (1H, d, *J* 10, 7-H), 3.55 (1H, m, 9-H), 3.46 (1H, m, 3-H), 3.38 (1H, m, 1-H), 2.83 – 2.67 (4H, m, 2"-H_2, 2"'-H_2), 2.20 (1H, m, 5-H), 2.08 (1H, m, 10-*H*H), 2.02 – 1.63 (6H, m, 6-H, 10-H*H*, 1"-H_2, 1"'-H_2), 1.55 (1H, m, 4-*H*H), 1.30 (1H, m, 4-H*H*); δ_C (100 MHz, $CDCl_3$) 142.1, 141.0, 137.4, 134.1 (C-1'), 128.5, 128.5, 128.3 (C-2'), 128.3, 128.2, 128.0, 128.0, 127.8, 126.5, 125.8, 125.7, 125.7, 83.3 (C-7), 79.1 (C-1), 75.7 (C-9), 75.0 (C-3), 50.6 (C-6), 41.9 (C-5), 40.3 (C-4), 38.1 (C-10), 37.6, 37. 5 (C-1" & C-1"'), 31.6, 31.3 (C-2" & C-2"'); Found (ESI) 551.2906 [MNa^+] ($C_{38}H_{40}O_2Na$ requires 551.2920).

3-(4-(Benzenesulfonyloxyphenyl)propional 98



97 **98**

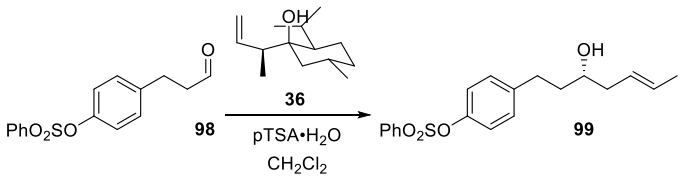
A suspension of acid **97** (8 g, 48.15 mmol), benzyl bromide (9.89 g, 57.78 mmol) and potassium hydrogen carbonate (7.23 g, 72.22 mmol) in acetone (50 mL) was heated to reflux for 12 h. Solvent was removed *in vacuo*, then CH_2Cl_2 (30 mL) and water (30 mL) were added. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by column chromatography using 10% of ethyl acetate in petroleum ether 40-60 °C to give benzyl ester as a pale-yellow oil (10.98 g, 89%).

Benzene sulfonyl chloride (8 g, 45.10 mmol) and triethylamine (4.35 mL, 42.92 mmol) were added dropwise to a stirring solution of benzyl ester (11 g, 42.92 mmol) in CH_2Cl_2 (72 mL) under nitrogen at 0 °C. After 5 min of stirring, the reaction mixture was allowed to warm to room temperature and stirred for 21 h. Saturated solution of NH_4Cl (70 mL) was added and the mixture was stirred for 10 min. The aqueous phase was extracted with CH_2Cl_2 (2 × 70 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was

purified by column chromatography using 5-10% ethyl acetate in petroleum ether 40-60 °C to give benzyl ester as a white solid (16.55 g, 99%).

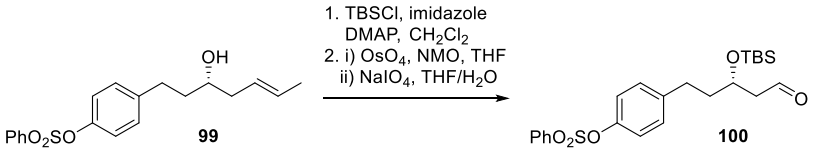
DIBALH (1 M, 11 mL, 11 mmol) was added dropwise to a solution of benzyl ester (2.12 g, 10.84 mmol) at −78 °C, under nitrogen, then stirred for 3 h. The reaction was allowed to warm to room temperature, then quenched with Rochelle's salt solution (350 mL) and stirred overnight. The reaction mixture was extracted with CH_2Cl_2 (2 × 400 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by column chromatography using 10% EtOAc in petroleum ether 40-60 °C to yield aldehyde **98** as a colourless oil (5.79 g, 70%). δ_H (400 MHz, $CDCl_3$) 9.79 (1H, t, *J* 2, 1-H), 7.85 – 7.80 (2H, m, OSO_2Ph), 6.66 (1H, m, OSO_2Ph), 7.56 – 7.49 (2H, m, OSO_2Ph), 7.12 – 7.08 (2H, m, Ar), 6.91 – 6.87 (2H, m, Ar), 2.91 (2H, t, *J* 7, 3-H_2), 2.75 (2H, t, *J* 7, 2-H_2); δ_C (100 MHz, $CDCl_3$) 201.0 (C-1), 148.0, 139.7, 135.5, 134.3, 129.6, 129.2, 128.5, 122.5, 45.0 (C-2), 27.4 (C-3). Spectroscopic data in accord with the literature.[41]

(*S, E*) 1-(4'-Benzenesulfonyloxyphenyl)-hept-5-en-3-ol 99



Nokami reagent **36** (5.1 g, 24.1 mmol) and *p*-toluenesulfonic acid hydrate (0.23 g, 1.2 mmol) were added to a solution of aldehyde **98** (3.5 g, 12.05 mmol) in CH_2Cl_2 (80 mL) under nitrogen. The reaction mixture was stirred at room temperature for 22 h. Water (80 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by column chromatography using 20% EtOAc in petroleum ether 40-60 °C to yield alcohol **99** as a colourless oil (3.67 g, 88%). $[\alpha]_D^{25}$ −8.0 (*c*. 1.0 $CHCl_3$) Lit[41] $[\alpha]_D^{20}$ −11.0 (*c* 1.0 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.86 – 7.80 (2H, m, OSO_2Ph), 7.71 – 7.60 (2H, m, OSO_2Ph), 7.57 – 7.46 (2H, m, OSO_2Ph), 7.10 (2H, d, *J* 9, Ar), 6.87 (2H, d, *J* 9, Ar), 5.55 (1H, m, 6-H), 5.4 (1H, m, 5-H), 3.56 (1H, m, 3-H), 2.76 (1H, m, 1-*H*H), 2.64 (1H, m, 1-H*H*), 2.22 (1H, m, 2-*H*H), 2.09 (1H, m, 2-H*H*), 1.76 – 1.61 (5H, m, 7-H_3, 4-H_2). δ_C (100 MHz, $CDCl_3$) 147.7, 141.5, 135.6, 134.2, 129.6, 129.5, 129.2, 128.6, 126.8, 122.2, 70.0 (C-3), 40.9 (C-2), 38.2 (C-4), 31.5 (C-1), 18.1 (C-7). Spectroscopic data in accord with the literature.[41]

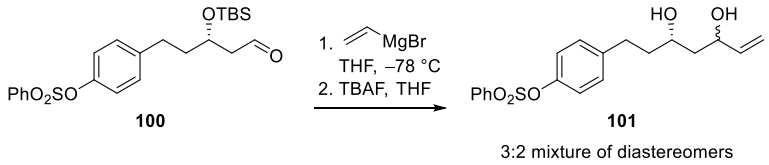
(*S*)-5-(4'-Benzenesulfonyloxyphenyl)-3-(*tert*butyldimethylsilyloxy)-pentanal 100



TBSCl (4.7 g, 31.18 mmol), imidazole (5.3 g, 77.94 mmol) and DMAP (0.32 g, 2.60 mmol) were added to a solution of alcohol **99** (9 g, 26 mmol) in dry CH_2Cl_2 (135 mL) under nitrogen. The reaction mixture was stirred at room temperature for 15 h, then quenched with the addition of water (70 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with a saturated solution of brine (50 mL), dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by column chromatography using 1% EtOAc in petroleum ether 40-60 °C to yield corresponding silyl ether as a colourless oil (10.73 g, 90%).

Silyl ether (2 g, 4.34 mmol) was dissolved in THF (45 mL) and *N*-methylmorpholine *N*-oxide (1.17 g, 8.68 mmol) and osmium tetroxide (3 crystals) were added under nitrogen. The reaction mixture was stirred at room temperature for 9 h, then quenched with a saturated solution of Na_2SO_3 (50 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo* to give a pale-yellow oil. Then, $NaIO_4$ (2.14 g, 10.0 mmol) was added to a solution of the crude oil in THF (200 mL) and water (200 mL). The reaction mixture was stirred for 4 h, then quenched with a saturated solution of $NaHCO_3$ (200 mL). The aqueous phase was extracted with EtOAc (3 × 200 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by column chromatography using 20% EtOAc in petroleum ether 40-60 °C to yield aldehyde **100** as a pale-yellow oil (1.87 g, 96%). δ_H (400 MHz, $CDCl_3$) 9.80 (1H, t, *J* 2, 1-H), 7.88 – 7.78 (2H, m, OSO_2Ph), 7.66 (1H, m, OSO_2Ph), 7.56 – 7.48 (2H, m, OSO_2Ph), 7.07 (1H, d, *J* 9, Ar), 6.88 (1H, d, *J* 9, Ar), 4.22 (1H, p, *J* 6, 3-H), 2.69 – 2.59 (2H, m, 2-H_2,), 2.57 (2H, ddd, *J* 6, 4, 2, 5-H_2), 1.83 – 1.76 (2H, m, 4-H_2), 0.88 (9H, s, $SiC(CH_3)_3$), 0.06 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 201.8 (C-1), 147.8, 141.0, 135.6, 134.2, 129.4, 129.2, 128.6, 122.4, 67.6 (C-3), 50.9 (C-2), 39.4 (C-4), 30.9 (C-5) 25.3 ($SiC(\mathit{C}H_3)_3$), 18.1 ($Si\mathit{C}(CH_3)_3$), −4.4 ($SiCH_3$), −4.5 ($SiCH_3$). Spectroscopic data in accord with the literature.[41]

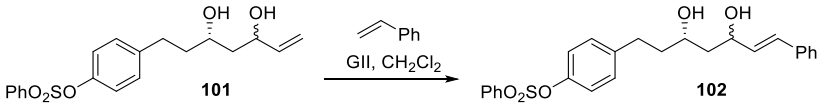
(*S*)-1-(4'-Benzenesulfonyloxyphenyl)-hept-6-ene-3,5-diol 101



Vinyl magnesium chloride (3.35 mL, 1 M in THF, 3.35 mmol) was added to a solution of aldehyde **100** (1 g, 2.23 mmol) in dry THF (7 mL) at −78 °C under nitrogen. The reaction mixture was stirred at this temperature for 3 h, then quenched with the addition of a saturated solution of NH_4Cl (7 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo* to give vinyl alcohol as a 3:2 mixture of diastereomers as a pale-yellow oil (1.06 g, 99%).ν_{max} (neat)/cm^{-1}: 3436, 2953, 2929, 2857, 1502; δ_H (400 MHz, $CDCl_3$) 7.88 – 7.80 (2H, m, OSO_2Ph), 7.68 (1H, m, OSO_2Ph), 7.58 – 7.47 (2H, m, OSO_2Ph), 7.11 – 7.03 (2H, m, Ar), 6.92 – 6.83 (2H, m, Ar), 5.84 (1H, dd, *J* 10, 6, 6-H), 5.26 (1H, dt, *J* 17, 2, 7-*H*H), 5.10 (1H, dt, *J* 10, 1, 7-H*H*), 4.27 (1H, m, 3-H), 3.97 (1H, m, 5-H), 2.61 (2H, m, 1-H_2), 1.90 – 1.64 (4H, m, 2-H_2, 4-H_2), 0.91 (9H, s, $SiC(CH_3)_3$), 0.09 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 147.6, 141.3, 140.8 (C-6), 135.5, 134.1, 129.3, 129.1, 128.5, 122.2, 114.3 (C-7), 71.5 (C-3), 71.3 (C-5), 43.2 (C-4), 39.3 (C-2), 30.4 (C-1), 25.8 ($SiC(CH_3)_3$), 17.9 ($SiC(CH_3)_3$), −4.1 ($SiCH_3$), −4.6 ($SiCH_3$); Found (ESI) 499.1945 [MNa^+] ($C_{25}H_{36}O_5SNa$ requires 499.1950).

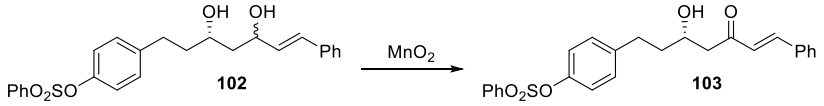
TBAF (19.72 mL, 1 M in THF, 19.72 mmol) was added to a solution of the mixture of diastereomers of silyl ether (1.98 g, 3.94 mmol) in dry THF (20 mL) under nitrogen. The reaction mixture was stirred at room temperature for 2 h, then quenched with water (20 mL). The aqueous phase was extracted with EtOAc (4 × 25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by column chromatography using 30% EtOAc in petroleum ether 40-60 °C to yield diol **101** as a 3:2 mixture of diastereomers as a yellow oil (0.98 g, 66%).ν_{max} (neat)/cm^{-1}: 3354, 2938, 2929, 1501, 1449; δ_H (400 MHz, $CDCl_3$) 7.88 – 7.78 (2H, m, OSO_2Ph), 7.67 (1H, m, OSO_2Ph), 7.58 – 7.46 (2H, m, OSO_2Ph), 7.15 – 7.04 (2H, m, Ar), 6.90 – 6.85 (2H, m, Ar), 5.87 (1H, ddd, *J* 17, 10, 6, 6-H), 5.24 (1H, dt, *J* 17, 1, 7-*H*H), 5.11 (1H, dt, *J* 10, 1, 7-H*H*), 4.36 (1H, m, 5-H), 3.87 (1H, m, 3-H), 2.80 – 2.57 (2H, m, 1-H_2), 1.85 – 1.60 (4H, m, 2-H_2, 4-H_2); δ_C (100 MHz, $CDCl_3$) 147.7, 141.3, 140.7 (C-6), 140.5, 134.2, 129.6, 129.6, 129.2, 128. 6, 122.7, 114.8 (C-7), 74.0 (C-5), 71.4 (C-3), 43.0 (C-4), 39.4 (C-2), 31.0 (C-1); Found (ESI) 385.1082 [MNa^+] ($C_{19}H_{22}OSNa$ requires 385.1086).

(*S*)-1-(4'-Benzenesulfonyloxyphenyl)-7-phenylhept-6-ene-3,5-diol 102



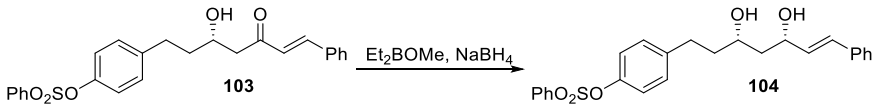
Styrene (0.95 g, 2.62 mmol) and Grubbs catalyst 2nd Generation (0.067 g, 0.079 mmol) were added to a solution of the mixture of diastereomer of diol **101** (0.48 g, 1.32 mmol) in dry CH_2Cl_2 (20 mL) under nitrogen. The stirring reaction mixture was heated to reflux for 3 h. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography using 30% EtOAc in petroleum ether 40-60 °C to yield diol **102** as a 5:2 mixture of diastereomers as a pale-yellow oil (0.41 g, 35%). Data for major diastereomer. ν_{max} (neat)/cm^{-1}: 3353, 3028, 2919, 1501, 1449; δ_H (400 MHz, $CDCl_3$) 7.89 – 7.78 (2H, m, OSO_2Ph), 7.66 (1H, m, OSO_2Ph), 7.56 – 7.49 (2H, m, OSO_2Ph), 7.25 (4H, m, Ar), 7.28 – 7.21 (1H, m, Ar), 7.13 – 7.06 (2H, m, Ar), 6.93 – 6.83 (2H, m, Ar), 6.59 (1H, d, *J* 15, 7-H), 6.22 (1H, dd, *J* 16, 7, 6-H), 4.55 (1H, q, *J* 7, 5-H), 3.93 (1H, m, 3-H), 2.84 – 2.59 (2H, m, 1-H_2), 1.87 – 1.69 (4H, m, 2-H_2, 4-H_2); δ_C (100 MHz, $CDCl_3$) 147.7, 141.2, 136.5, 135.6, 134.2, 131.7 (C-6), 130.4 (C-7), 129.6, 129.2, 128.7, 128.6, 127.9, 126.6, 122.3, 73.8 (C-5), 71.4 (C-3), 43.3 (C-4), 39.5 (C-2), 31.1 (C-1); Found (ESI) 461.1398 [MNa^+] ($C_{25}H_{26}O_5SNa$ requires 461.1393).

(*S*)-1-(4'-Benzenesulfonyloxyphenyl)-7-phenylhept-6-ene-5-one-3-ol. 103



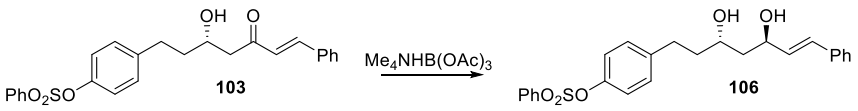
MnO_2 (0.42 g, .958 mmol) was added to a solution of diol **102** in CH_2Cl_2. The reaction mixture was stirred at room temperature for 3 h, then filtered through celite and the solvent evaporated *in vacuo*. The residue was purified by column chromatography using 30-50% EtOAc in petroleum ether 40-60 °C to yield ketone **103** as a pale-yellow oil (0.27 g, 64%). $[\alpha]_D^{21}$ +3.5 (*c* 1.0 $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3453, 3062, 2926, 1705, 1648, 1606, 1501; δ_H (400 MHz, $CDCl_3$) 7.85 – 7.81 (2H, m, OSO_2Ph), 7.68 – 7.63 (1H, m, OSO_2Ph), 7.59 – 7.48 (5H, m, OSO_2Ph, Ar, 7-H), 7.46 – 7.35 (3H, m, Ar), 7.11 (1H, m, Ar), 6.88 (2H, m, Ar), 6.71 (1H, d, *J* 16, 6-H), 4.10 (1H, m, 3-H), 3.34 (1H, s, OH), 2.93 – 2.62 (4H, m, 2-H_2, 4-H_2), 1.83 (1H, m, 2-*H*H), 1.71 (1H, m, 2-H*H*); δ_C (100 MHz, $CDCl_3$) 200.8 (C-5), 147.8, 143.9 (C-7), 141.2, 135.6, 134.2, 134.2, 131.0, 129.7, 129.2, 129.1, 128.6, 128.5, 126.3 (C-6), 122.3, 67.0 (C-3), 46.9 (C-4), 38.0 (C-2), 31.2 (C-1); Found (ESI) 459.1226 [MNa^+] ($C_{25}H_{24}O_5SNa$ 459.1237 requires).

(+)-(3*S,5S,E*)-1-(4'-Benzenesulfonyloxyphenyl)-7-phenylhept-6-ene-3,5-ol 104



Diethyl methoxy borane (0.034 mL, 0.254 mmol) was added to a solution of hydroxyketone **103** (0.101g, 0.231 mmol) in a mixture of THF (8 mL) and MeOH (2 ml), at −78 °C, under N_2. The mixture was stirred at this temperature for 30 min, then $NaBH_4$ (0.01, 0.28 mmol) was added. The mixture reaction was stirred for 5 h then quenched with 2.5M NaOH solution (4 mL) and hydrogen peroxide (2 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo* to yield *syn*-diol **104** as single diastereomer as a colourless oil (0.10 mg, 99%). $[\alpha]_D^{21}$ +3.0 (*c* 1.0 $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3286, 2916, 1502, 1449, 1372; δ_H (400 MHz, $CDCl_3$) 7.86 – 7.80 (2H, m, OSO_2Ph), 7.69 – 7.63 (1H, m, OSO_2Ph), 7.55 – 7.48 (2H m, OSO_2Ph), 7.39 – 7.28 (4H, m, Ar), 7.26 – 7.21 (1H, m, Ar), 7.13 – 7.08 (2H, m, Ar), 6.91 – 6.83 (2H, m, Ar), 6.59 (1H, d, *J* 16, 7-H), 6.21 (1H, dd, *J* 16, 7, 6-H), 4.54 (1H, q, *J* 7, 5-H), 3.92 (1H, m, 3-H), 2.82 – 2.59 (2H, m, 1-H_2), 1.84 – 1.68 (4H, m, 2-H_2, 4-H_2); δ_C (100 MHz, $CDCl_3$) 147.8, 141.2, 136.5, 135.6, 134.2, 131.7 (C-6), 130.4 (C-7), 129.6, 129.2, 128.7, 128.6, 127.9, 126.6, 122.3, 73.8 (C-5), 71.4 (C-3), 43.4 (C-4), 39.5 (C-2), 31.1 (C-1); Found (ESI) 461.1395 [MNa^+] ($C_{25}H_{26}O_5SNa$ requires 461.1393).

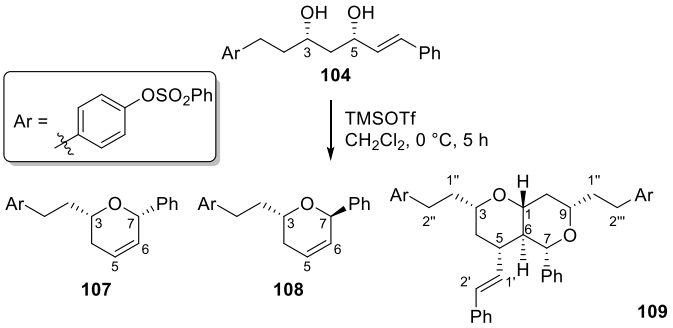
(–)-(3*S,5R,E*)-1-(4'-Benzenesulfonyloxyphenyl)-7-phenylhept-6-ene-3,5-diol 106



Glacial acetic acid (10 mL) was added to a solution of $Me_4NHB(OAc)_3$ (603 mg, 2.29 mmol) in anhydrous acetonitrile (10 mL) and the mixture stirred at room temperature under an atmosphere of nitrogen for 30 min. The borohydride solution was then added by cannula to a solution of hydroxyketone **103** (0.125 mg, 0.286 mmol) in dry acetonitrile (10 mL) at −20 °C and stirred for 3 h. The reaction was quenched with saturated solution of Rochelle's salt (20 mL) and allowed to warm to room temperature whilst vigorously stirring for 1 h. The reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (7 × 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by column chromatography using 20-40% EtOAc in petroleum ether 40-60 °C to yield *anti*-diol **106** as a 7:1 mixture of diastereomers as a colourless oil (0.107, 85%). $[\alpha]_D^{21}$ –3.0 (*c* 1.0 $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3369, 2940, 1501, 1449,

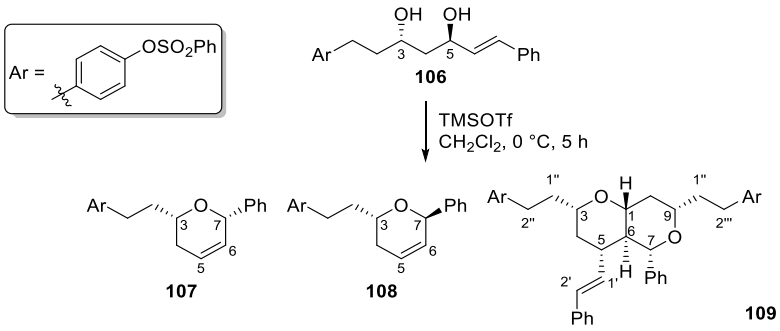
1371; δ_H (400 MHz, $CDCl_3$) 7.87 – 7.77 (2H, m, OSO_2Ph), 7.68 – 7.62 (1H, m, OSO_2Ph), 7.54 – 7.47 (2H, m, OSO_2Ph), 7.39 – 7.28 (4H, m, Ar), 7.25 – 7.21 (1H, m, Ar), 7.12 – 7.05 (2H, m, Ar), 6.92 – 6.83 (2H, m, Ar), 6.61 (1H, d, *J* 16, 7-H), 6.26 (1H, dd, *J* 16, 6, 6-H), 4.65 (1H, q, *J* 6, 5-H), 3.97 (1H, m, 3-H), 2.80 – 2.57 (2H, m, 1-H_2), 1.87 – 1.68 (4H, m, 2-H_2, 4-H_2); δ_C (100 MHz, $CDCl_3$) 147.8, 141.2, 136.6, 135.6, 134.2, 131.8 (C-6), 130.3 (C-7), 129.6, 129.2, 128.6, 128.6, 127.9, 126.5, 122.3, 70.7 (C-5), 68.6 (C-3), 42.8 (C-4), 39.1 (C-2), 31.5 (C-1)); Found (ESI) 461.1393 [MNa^+] ($C_{25}H_{26}O_5SNa$ requires 461.1393).

Treatment of 3,5-*syn*-diol 104 with TMSOTf



Diol **104** (0.11 g, 0.25 mmol) in anhydrous CH_2Cl_2 (2.5 mL) under nitrogen and the solution was cooled to 0 °C. TMSOTf (2 µL, 0.012 mmol) was added and the mixture stirred at this temperature for 5 h. Water (2.5 mL) was added and the two phases separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The crude product was purified by column chromatography. Elution with 1% EtOAc in petroleum ether 40-60 °C gave *syn*-dihydropyran **107** (13 mg, 12%) and *anti*-dihydropyran **108** (5 mg, 5 % yield), elution with 5% EtOAc in petroleum ether 40-60 °C gave blepharocalyxin analogue **109** (17.6 mg, 17% yield) and finally using 20% EtOAc in petroleum ether 40-60 °C a further mixture of dimeric diarylheptanoids (14.6 mg, 14% yield) was obtained.

Treatment of 3,5-*anti*-diol 106 with TMSOTf



Diol **106** (0.13 g, 0.29 mmol) in anhydrous CH_2Cl_2 (3 mL) under nitrogen and the solution was cooled to 0 °C. TMSOTf (2.6 µL, 0.014 mmol) was added and the mixture stirred at this temperature for 5 h. Water (2 mL) was added and the two phases separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The crude product was purified by column chromatography. Elution with 1% EtOAc in petroleum ether 40-60 °C gave *syn*-dihydropyran **107** (6 mg, 5%) and *anti*-dihydropyran **108** (19 mg, 15 % yield), elution with 5% EtOAc in petroleum ether 40-60 °C gave blepharocalyxin analogue **109** (38 mg, 31% yield) and finally using 20% EtOAc in petroleum ether 40-60 °C a further mixture of dimeric diarylheptanoids (17.4 mg, 14% yield) was obtained.

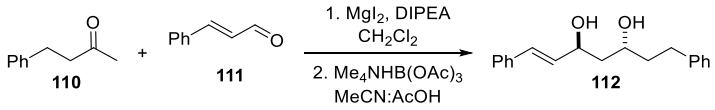
(3*S*,7*S*)-3-(*p*-phenyl benzenesulfonate)-7-phenyl-3,4-dihydro-2H-pyran 107. A colourless oil. ν_{max} (neat)/cm^{-1} 3062, 2925, 2859, 1689, 1501: δ_H (400 MHz, $CDCl_3$) 7.84 – 7.81 (2H, m, Ar), 7.68 – 7.63 (1H, m Ar), 7.54 – 7.49 (2H, m, Ar), 7.39 – 7.33 (4H, m, Ar), 7.31 – 7.27 (1H, m, Ar), 7.12 – 7.07 (2H, m, Ar). 6.89 – 6.86 (2H,m, Ar), 5.90 (1H, m, 5-H), 5.75 (1H, m, 6-H), 5.10 (1H, m, 7-H), 3.65 (1H, m, 3-H), 2.82 – 2.66 (2H, m, 1-H_2), 2.13 (1H, m, 4-*H*H), 2.03 – 1.87 (2H, m, 4-H*H*, 2-*H*H), 1.77 (1H, m, 2-H*H*); δ_C (100 MHz, $CDCl_3$) 147.7, 141.7, 141.4, 135.6, 134.2, 130.2 (C-6), 129.6, 129.1, 128.6, 128.6, 127.8, 127.2, 124.7 (C-5), 122.2, 77.7 (C-7), 73.2 (C-3), 37.3 (C-2), 31.0 (C-1), 31.0 (C-4). Found (ESI) 443.1283 [MNa^+] ($C_{25}H_{24}O_4SNa$ requires 443.1288).

(3*S*,7*R*)-3-(*p*-phenyl benzenesulfonate)-7-phenyl-3,4-dihydro-2H-pyran 108. A colourless oil. ν_{max} (neat)/cm^{-1} 3032, 2925, 2863, 1691, 1501; δ_H (400 MHz, $CDCl_3$) 7.82 – 7.79 (2H, m, Ar), 7.68 – 7.64 (1H, m Ar), 7.53 – 7.49 (2H, m, Ar), 7.40 – 7.29 (5H, m, Ar), 6.76 – 6.70 (4H, m, Ar), 6.04 (1H, m, 5-H), 5.99 (1H, m, 6-H), 5.27 (1H, s (br), 7-H), 3.43 (1H, m, 3-H), 2.65 (1H, m, 1-*H*H), 2.46 (1H, dt, *J* 14, 8, 8, 1-H*H*), 2.06 (1H, ddq, *J* 17, 10, 2, 4-*H*H), 1.96 (1H, m, 4-H*H*), 1.81 (1H, m, 2-*H*H), 1.60 (1H, m, 2-H*H*); δ_C (100 MHz, $CDCl_3$) 147.5, 141.3, 141.0, 135.6, 134.1, 129.7, 129.1, 128.6, 128.5, 128.4, 127.8, 127.4 (C-6), 126.1 (C-5), 122.0, 74.3 (C-7), 65.9 (C-3), 37.2 (C-2), 31.2 (C-1), 30.9 (C-4). Found (ESI) 443.1280 [MNa^+] ($C_{25}H_{24}O_4SNa$ requires 443.1287).

(1*R*,3*S*,5*S*,6*S*,7*S*,9*S)*-3,9-(*p*-phenylbenzenesulfonate)-7-phenyl-5((*E*)-phenethenyl)-2,8-dioxabicyclo[4.4.0]decane 109. A colourless oil. ν_{max} (neat)/cm^{-1} 3026, 2924, 1502; δ_H (500 MHz, $CDCl_3$) 7.85 – 7.81 (4H, m, Ar), 7.68 – 7.63 (2H, m, Ar), 7.54 – 7.50 (4H, m, Ar), 7.33 – 7.03 (11H, m, Ar), 6.97 (1H, m, Ar), 6.89 – 6.84 (4H, m, Ar), 6.71 – 6.7 (2H, m, Ar), 5.81 (1H, d, *J* 16, 2'-H), 5.11 (1H, dd, *J* 16, 9, 1'-H), 3.98 (1H, d, *J* 10, 7-H), 3.49 (1H, m, 9-H), 3.42 (1H, m, 3-H), 3.34 (1H, m, 1-H), 2.76 – 2.59 (4H, m, 2"-H_2, 2"'-H_2), 2.18 (1H, m, 5-H), 1.99 (1H, m, 10-*H*H), 1.88 (1H, m, 1'''-*H*H), 1.83 – 1.72 (2H, m, 1''-*H*H, 1'''-H*H*), 1.68 – 1.60 (3H, m, 6-H, 10-H*H,* 1"'-H*H*), 1.51

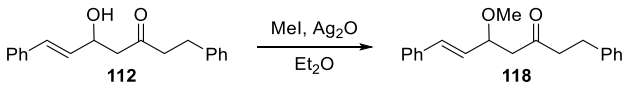
(1H, m, 4-*H*H), 1.32 (1H, m, 4-H*H*); δ_C (100 MHz, $CDCl_3$) 147.61, 147.60, 141.2, 140.8 (C-1'), 137.3, 135.6, 135.5, 134.1, 133.9, 129.6, 129.5, 128.5, 128.2 (C-2'), 128.1, 128.0, 127.8, 126.6, 125.8, 122.1, 122.0, 83.4 (C-7), 79.1 (C-1), 75.6 (C-3), 74.8 (C-9), 50.6 (C-6), 41.9 (C-5), 40.3 (C-4), 38.1 (C-10), 37.4 (C-1''), 37.2 (C-1'''), 31.0 (C-2"), 30.1 (C-2'''); Found (ESI) 863.2665 [MNa^+] ($C_{50}H_{48}O_8S_2Na$ requires 863.2683).

(±)-(1*E*, 3*S,5*R**)-1,7-Diphenylhept-1-ene-3,5-diol 112**



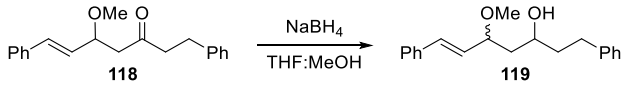
Cinnamaldehyde (0.48 mL 3.78 mmol), benzylacetone (0.68 mL, 4.54 mmol) and MgI_2 (1.26 g, 4.54 mmol) were dissolved in anhydrous CH_2Cl_2 (20 mL) under nitrogen and the flask protected from light. *N*,*N*-Diisopropylethylamine (0.85 mL, 4.92 mmol) was added by syringe pump at 0.85 mL/min. The reaction mixture was stirred for 1 h at room temperature and quenched with saturated solution of $NaHCO_3$ (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was purified by column chromatography using 10% EtOAc in petroleum ether 40-60 °C to give an inseparable 10:1 mixture of regioisomers. $Me_4NHB(OAc)_3$ (4.23g, 20 mmol) was dissolved in dry MeCN (12 mL) and glacial acetic acid (12 mL) under nitrogen. The mixture was stirred for 30 min at room temperature, then cooled to −40 °C and a solution of the mixture of regioisomers (0.70 mg, 2.5 mmol) in dry MeCN (3.5 mL) was added. The reaction mixture was warmed −20 °C and stirred overnight. The reaction was quenched with Rochelle's salt solution (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic layers were washed with $NaHCO_{3(aq)}$ (3 × 25 mL). The organic phase was dried over $MgSO_4$, and solvent evaporated *in vacuo*. The residue was purified by column chromatography using 10-20% EtOAc in petroleum ether 40-60 °C to give diol **112** as pale-yellow oil (0.48 g, 45% over two steps). δ_H (400 MHz, $CDCl_3$) 7.39 – 7.16 (10H, m, Ar), 6.63 (1H, d, *J* 16, 1-H), 6.28 (1H, dd, *J* 16, 6, 2-H), 4.67 (1H, q, *J* 5, 3-H), 4.03 (1H, m, 5-H), 2.81 (1H, m, 7-*H*H), 2.69 (1H, m, 7-H*H*), 1.94 – 1.75 (4H, m, 6-H_2, 4-H_2); δ_C (100 MHz, $CDCl_3$) 142.0, 136.7, 132.0 (C-2), 130.3 (C-1), 128.8, 128.6, 128.5, 127.9, 126.6, 126.0, 70.8 (C-3), 69.1 (C-5), 42.8 (C-4), 39.4 (C-6), 32.3 (C-7). Spectroscopic data in accord with the literature.[116]

(±)-(*E*)-5-Methoxy-1,7-diphenylhept-6-en-3-one 118



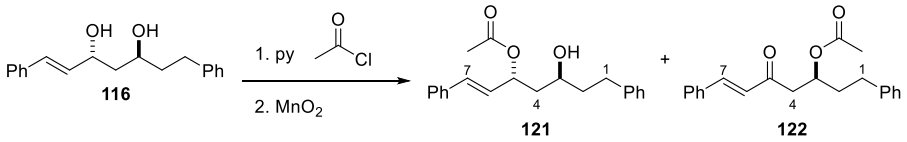
Silver(I) oxide (3.10 g, 13.4 mmol) and MeI (2.28 mL, 53.5 mmol) were added to a solution of β-hydroxyketone **112** (1.5 g, 5.35 mmol) in dry Et_2O (27 mL) under nitrogen. The reaction was protected from light and stirred for 3 days. The reaction mixture was then filtered through celite, washed with EtOAc (100 mL) and concentrated *in vacuo*. The crude product was purified by column chromatography using 2-10 % EtOAc in petrol ether 40-60 °C to afford β-methoxy ketone **118** (0.949 g, 60 %) as a pale-yellow oil. ν_{max} (neat)/cm^{-1} 3060 (w), 3026 (w), 2929 (w), 2822 (w), 1713 (s), 1677 (s); δ_H (400 MHz, $CDCl_3$) 7.14 – 7.42 (10H, m, Ar), 6.59 (1H, d, *J* 16, 7-H), 6.04 (1H, dd, *J* 16, 8, 6-H), 4.19 – 4.28 (1H, m, 5-H), 3.29 (3H, s, OCH_3), 2.73 – 2.95 (5H, m, 1-H_2, 2-H_2, 4-H*H*), 2.54 (1H, dd, *J* 16, 5, 4-*H*H); δ_C (100 MHz, $CDCl_3$) 207.5 (C-3), 132.7 (C-7), 128.5, 128.4 (C-6), 128.3, 127.9, 126.5, 126.0, 78.3 (C-5), 56.5 (OCH_3), 49.0 (C-4), 45.5 (C-2), 29.4 (C-1); Found (ESI) 317.1513 [MNa^+] ($C_{20}H_{22}NaO_2$ requires 317.1512).

(±)-(*E*)-5-methoxy-1,7-diphenylhept-6-en-3-ol 119



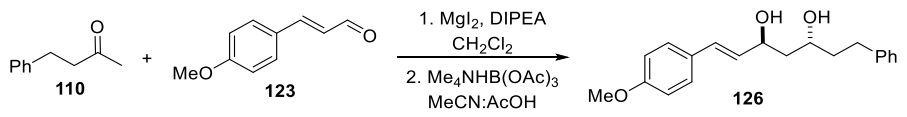
$NaBH_4$ (0.843 g, 31.9 mmol) was carefully added to a solution of **118** (0.94 g, 3.19 mmol) in 1:1 THF:MeOH (110 mL) at 0 °C. After 30 minutes the reaction was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by the addition of saturated NH_4Cl solution (55 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography using 10 % EtOAc in petrol ether 40-60 °C to yield alcohol **119** (0.94 g, 99 %) as a colourless oil and a 3:2 mixture of diastereomers. ν_{max} (neat)/cm^{-1}: 3412 (br), 3025 (w), 2929 (w), 2858 (w) , 1494 (s); δ_H (400 MHz, $CDCl_3$) 7.15 – 7.41 (10H, m, Ar), 6.57 (1H, dd, *J* 16, 7-H), 6.13 (1H, dd, *J* 16, 8, 6-H), 3.78 – 4.10 (2H, m, 3-H, 5-H), 3.34 (3H, s, OCH_3), 2.59 – 2.88 (2H, m, 1-H), 1.63 – 1.89 (4H, m, 2-H, 4-H); δ_C (100 MHz, $CDCl_3$) 142.4, 136.3, 132.9 (C-7), 129.2 (C-6), 128.8, 128.5, 126.7, 128.1, 125.9, 83.7 (C-5), 70.9 (C-3), 56.3 (OCH_3), 42.9 (C-4), 39.4 (C-2), 31.9 (C-1); Found (ESI) 319.1668 [$MNa]^+$ ($C_{20}H_{24}NaO_2$ requires 319.1668).

(±)-(6*E*, 3*S,5*R**)-(*E*)-5-acetoxy-1,7-diphenylhept-6-en-3-ol 121 and (±)-(6*E*, 3*S**,5*R**)-(*E*)-5-acetoxy-1,7-diphenylhept-6-en-3-ol 122**



Diol **116** (1 g, 3.54 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and pyridine (0.3 mL, 3.54 mmol) and acetyl chloride (0.20 mL, 2.83 mmol) were added dropwise under nitrogen. The reaction was stirred at room temperature for 25 min. Water (10 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 5-40% EtOAc in petroleum ether 40-60 °C to give a 3:1 mixture of monoacetylated compounds. The mixture of acetates was dissolved in CH_2Cl_2 (22 mL) and MnO_2 (1.25 g, 33.83 mmol) was added. The reaction mixture was stirred at room temperature overnight. The crude reaction was filtered through celite and the solvent removed *in vacuo*. The residue was purified by column chromatography using 5-15% EtOAc in petroleum ether 40-60 °C to give alcohol **121** (0.51 g, 45% over two steps) and ketone **122** (0.19 g, 16%) as colourless oils. Alcohol **121** ν_{max} (neat)/cm^{-1}: 3442, 3025, 2922, 2858, 1732; δ_H (400 MHz, $CDCl_3$)7.41 – 7.20 (10H, m, Ar), 6.65 (1H, d, *J* 16, 1-H), 6.22 (1H, dd, *J* 16, 7, 2-H), 5.73 (1H, m, 3-H), 3.64 (1H, m, 5-H), 2.86 (1H, m, 7-*H*H), 2.72(1H, m, 7-H*H*) 2.13 (3H, s, CH_3), 1.92-1.74 (4H, m, 6-H_2, 4-H_2); δ_C (100 MHz, $CDCl_3$) 171.5 (CO), 142.03, 136.1, 132.1 (C-1), 128.6, 128.5, 128.4, 128.1, 127.4 (C-2) 126.6, 125.8, 72.1 (C-3), 66.7 (C-5), 43.1 (C-6), 38.8 (C-4), 32.1 (C-7), 21.2 (CH_3); Found (ESI) 347.1611[MNa^+] ($C_{21}H_{24}O_3Na$ requires 347.1618). Ketone **122**. δ_H (400 MHz, $CDCl_3$) 7.57 (1H, d, *J* 16, 7-H), 7.56 – 7.53 (2H, m, Ar), 7.42 – 7.38 (3H, m, Ar), 7.31 – 7.26 (2H, m, Ar), 7.22 – 7.16 (3H, m, Ar), 6.72 (1H, d, *J* 16, 6-H), 5.38 (1H, p, *J* 6, 3-H), 3.07 (1H, dd, *J* 15, 6, 4-*H*H), 2.85 (1H, dd, *J* 15, 6, 4-H*H*), 2.77 – 2.63 (2H, qt, *J* 14, 8, 1-H_2), 2.32 –1.97 (2H, td, *J* 8, 6, 2-H_2), 2.02 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 196.9 (CO), 170.5, 143.5 (C-7), 141.2, 134.3, 130.7, 129.0, 128.5, 128.4, 128.3, 126.0 (C-6), 70.6 (C-3), 45.1 (C-4), 35.7 (C-1), 31.7 (C-2), 21.1 (CH_3).

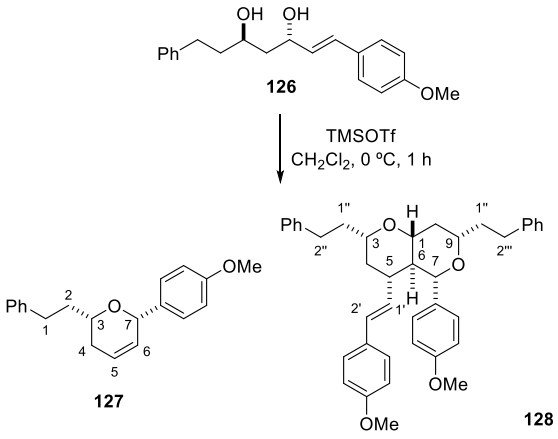
(1*E*, 3*S, 5*R**)-1-(*p*-methoxyphenyl)-7-phenylhept-1-ene-3,5-diol 126**



p-Methoxycinnamaldehyde **123** (2.50 g, 15.41 mmol), benzylacetone (2.74 g, 18.49 mmol) and MgI_2 (2.59 g, 2.04 mmol) were dissolved in dry CH_2Cl_2 (77 mL) under nitrogen and the flask

protected from light. *N*,*N*-Diisopropylethylamine (3.49 mL, 20.01 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h, quenched by the addition of saturated $NaHCO_3$ solution (80 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The residue was purified by column chromatography using 5-20% EtOAc in petroleum ether 40-60 °C to give and inseparable mixture 16:1 of regioisomers as orange oil. $Me_4NHB(OAc)_3$ (13.66 g, 64.48 mmol) was dissolved in dry MeCN (50 mL) and glacial acetic acid (50 mL) and the mixture stirred for 30 min at room temperature under nitrogen. The solution was cooled down to −40 °C and a solution of the regioisomer mixture (4 g, 12.89 mmol) in dry MeCN (12.5 mL) was added dropwise, then the mixture was warmed to −20 °C and stirred overnight. The reaction was quenched with the addition of 0.5N sodium tartare solution (80 mL) and diluted with CH_2Cl_2 (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), the organic layers were washed with saturated $NaHCO_3$ solution (5 × 50 mL), dried over $MgSO_4$, and solvent evaporated *in vacuo*. The residue was purified by column chromatography using 10-40% EtOAc in petroleum ether 40-60 °C to give diol **126** as bright orange oil (1.78 g, 37% over two steps). ν_{max} (neat)/cm^{-1}: 3369 (br), 3029 (w), 2916 (w), 2836 (w), 1607 (m), 1513 (s); δ_H (400 MHz, $CDCl_3$) 7.34 – 7.26 (4H, m, Ar), 7.21 – 7.16 (3H, m, Ar), 6.86 (2H, d, *J* 9, Ar), 6.56 (2H, d, *J* 16, 1-H), 6.14 (1H, dd, *J* 16, 6, 2-H), 4.63 (1H, m, 3-H), 4.04 (1H, m, 5-H), 3.81 (3H, s, OCH_3), 2.80 (1H, m, 7-*H*H), 2.68 (1H, m, 7-H*H*), 1.93 – 1.74 (4H, m, 4-H_2, 6-H_2); δ_C (100 MHz, $CDCl_3$) 159.4 , 142.1 , 129.9 (C-2), 129.7 (C-1), 129.4 , 128.6 , 128.5 , 127.8 , 126.0 , 114.2 , 71.0 (C-3), 69.0 (C-5), 55.4 (OCH_3), 42.9 (C-4), 39.3 (C-6), 32.3 (C-7); Found (ESI) 335.1617 [MNa^+] ($C_{25}H_{26}O_5SNa$ requires 335.1624).

Treatment of racemic diol 126 with TMSOTf



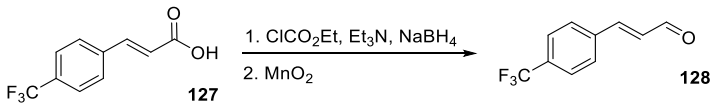
Diol **126** (0.40 mg, 1.28 mmol) was dissolved in CH_2Cl_2 (2.5 mL) under nitrogen and the solution was cooled to 0 °C. TMSOTf (12 µL, 0.064 mmol) was added and the mixture was stirred at this

temperature for 1 h. Water (3 mL) was added and the two phases separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The crude product was purified by column chromatography. Elution with 5% EtOAc in petroleum ether 40-60 °C gave *syn*-dihydropyran **127** (9 mg, 2% yield), elution with 10% EtOAc in petroleum ether 40-60 °C gave blepharocalyxin analogue **128** (86 mg, 23% yield) and finally using 30% EtOAc in petroleum ether 40-60 °C a further mixture of dimeric diarylheptanoids (121 mg, 32% yield) was obtained .

(3*S*,7*S*)-3-phenethyl-7-(*p*-methoxyphenyl)-3,4-dihydro-2H-pyran 127. A colourless oil. ν_{max} (neat)/cm^{-1}: 3063, 3026, 2929, 2841, 1678, 1599; δ_H (400 MHz, $CDCl_3$) 7.33 – 7.26 (4H, m, Ar), 7.22 – 7.17 (3H, m, Ar), 6.90 (2H, d, *J* 9, Ar), 5.91 (1H, m, 5-H), 5.74 (1H, m, 6-H), 5.10 (1H, m, 7-H), 3.81 (3H, s, OCH_3), 3.70 (1H, m, 3-H), 2.86 – 2.70 (2H, m, 1-H_2), 2.14 (1H, m, 4-*H*H), 2.04 – 1.93 (2H, m, 4-H*H*, 2-*H*H), 1.81 (1H, m, 2-H*H*); δ_C (100 MHz, $CDCl_3$) 159.2, 142.2, 133.9 (C-6), 130.3, 128.5, 128.5, 128.3, 125.7, 124.8 (C-5), 113.9, 77.1 (C-7), 73.3 (C-3), 55.3 (OCH_3), 37.4 (C-2), 31.6 (C-1), 31.0 (C-4). Found (ESI) 295.1691 [MH^+] ($C_{20}H_{22}O_2$ requires 295.1693).

(±)-(1*R,3*S**,5*S**,6*S**,7*S**,9*S**)-3,9-di(phenethyl)-5-(*E*)-(*p*-methoxyphen)ethenyl-7-(*p*-methoxy)phenyl-2,8-dioxabicyclo[4.4.0]decane 128**. A white solid. ν_{max} (neat)/cm^{-1}: 3024, 2911, 2844, 1603, 1512; δ_H (500 MHz, $CDCl_3$) 7.33 – 7.28 (5H, m, Ar), 7.23 – 7.19 (7H, m, Ar), 6.76 – 6.70 (4H, m, Ar), 5.75 (1H, d, *J* 16, 2'-H), 5.03 (1H, dd, *J* 16, 9, 1'-H), 4.00 (1H, d, *J* 10, 7-H), 3.80 (3H, s, OCH_3), 3.57 (1H, m, 9-H), 3.52 (3H, m, OCH_3), 3.47 (1H, m, 3-H), 3.38 (1H, m, 1-H), 2.81 (1H, m, 2"-*H*H), 2.76 – 2.70 (3H, 2'''-H_2, 2''-H*H*), 2.16 (1H, m, 5-H), 2.09 (1H, ddd, *J* 12, 4, 2, 10-*H*H), 2.00 (1H, m, 1'''-*H*H), 1.94 – 1.81 (2H, m, 1''-H*H*, 1'''-*H*H), 1.75 – 1.61 (3H, m, 1''-H*H*, 10-H*H*, 6-H), 1.57 (1H, m, 4-*H*H), 1.33 (1H, m, 4-H*H*); δ_C (125 MHz, $CDCl_3$) 159.1, 158.4, 142.2, 133.3, 132.2 (C-1'), 130.5, 128.5, 128.5, 128.3, 128.3, 127.0 (C-2'), 126.8, 125.7, 125.7, 113.3, 82.8 (C-7), 79.2 (C-1), 75.8 (C-3), 74.9 (C-9), 55.3 (OCH_3), 54.9 (OCH_3), 50.1 (C-6), 42.0 (C-5), 40.4 (C-4), 38.2 (C-10), 37.7, 37.5 (C-1" & C-1"'), 31.6, 31.4 (C-2" & C-2"'); Found (ESI) [MNa^+] 611.3157 ($C_{40}H_{44}O_4Na$ requires 611.3132).

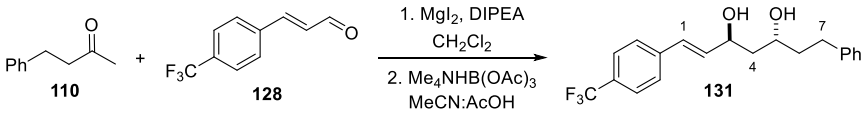
(*E*)-3-(4-(Trifluoromethyl)phenyl)-2-ene-1-propanol 128



4-(Trifluoromethyl)cinnamic acid **127** (0.5 g, 2.31 mmol) was dissolved in anhydrous THF (8 mL) under nitrogen and Et_3N (0.65 mL, 4.62 mmol) was added and the solution cooled to 0 °C. Ethyl

chloroformate (0.30 mL, 3.00 mmol) was added dropwise and the reaction was stirred at this temperature for 0.5 h. The mixture was filtered through celite and washed with EtOAc (15 mL). The filtrate was concentrated *in vacuo* and dissolved in MeOH (16 mL). $NaBH_4$ (0.22 g, 5.78 mmol) was added in portions at −78 °C and the solution was stirred for 1.5 h. The reaction was quenched with the addition of $NH_4Cl_{(aq)}$ (16 mL) and the mixture extracted with EtOAc (3 × 20 mL). The crude reaction was concentrated and suspended in CH_2Cl_2 (25 mL) and MnO_2 (3.61 g, 41.55 mmol) was added and the reaction stirred for 2h. The mixture was filtered through celite and rinse with CH_2Cl_2. The solvent was removed *in vacuo* to give compound **128** as white solid (0.39 g, 84%). δ_H (400 MHz, $CDCl_3$) 9.76 (1H, d, *J* 7.5, 1-H), 7.72 – 7.66 (4H, m, Ar), 7.51 (1H, d, *J* 16, 3-H), 6.78 (1H, dd, *J* 16, 7.5, 2-H); δ_C (100 MHz, $CDCl_3$) 193.1 (C-1), 150.2 (C-3), 130.5 (C-2), 128.6 , 126.1 (q, *J* 4, CF_3). Spectroscopic data in accord with the literature.[117]

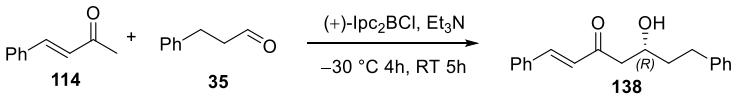
(1*E*, 3*S, 5*R**)-1-(*p*-trifluoromethylphenyl)-7-phenylhept-1-ene-3,5-diol 131**



Aldehyde **128** (1.40 g, 6.99 mmol), benzylacetone (1.26 mL, 8.39 mmol) and MgI_2 (2.34 g, 8.39 mmol) were dissolved in CH_2Cl_2 (35 mL) under nitrogen and the flask protected from light. *N*,*N*-Diisopropylethylamine (1.58 mL, 9.09 mmol) was added by syringe pump at 0.85 ml/min. The mixture was stirred at room temperature for 2 h and quenched with the addition of $NaHCO_{3(aq)}$ (35 mL). The mixture was extracted with CH_2Cl_2 (2 × 25 mL). The organic phase was dried over $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 5% EtOAc in petroleum ether 40-60 °C to give an inseparable 20:1 mixture of regioisomers (1.55 g). $Me_4NHB(OAc)_3$ (8.2 g, 38.65 mmol) was dissolved in dry MeCN (20 mL) and glacial acetic acid (20 mL) under nitrogen. The solution was cooled to −40 °C and a solution of the mixture of regioisomers in MeCN (10 mL) was added. The reaction mixture was allowed to warm to −20 °C and stirred overnight. The reaction was quenched with Rochelle's salt solution (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic layers were washed with $NaHCO_{3(aq)}$ repeatedly (8 × 10 mL). The organic phase was dried over $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 5-40% EtOAc in petroleum ether 40-60 °C to give diol **131** as a colourless oil (0.51 g, 20% over two steps). ν_{max} (neat)/cm^{-1}: 3287, 2943, 1614; δ_H (400 MHz, $CDCl_3$) 7.57 (2H, d, *J* 8, Ar), 7.45 (2H, d, *J* 8, Ar), 7.31 – 7.25 (2H, m, Ar), 7.22 – 7.17 (3H, m. Ar), 6.67 (1H, d, *J* 16, 1-H), 6.36 (1H, dd, 16, 6, 2-H), 4.69 (1H, m, 3-H), 4.03 (1H, m, 5-H), 2.80 (1H, m, 7-*H*H), 2.69 (1H, m, 7-H*H*), 1.95 – 1.76

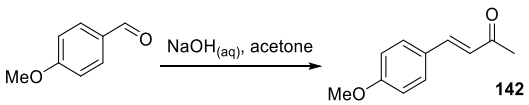
(4H, m, 6-H_2, 4-H_2); δ_C (100 MHz, $CDCl_3$) 141.8, 140.3, 134.8 (C-2), 128.6, 128.6 (C-1), 128.5 126.7, 126.1, 125.7 (q, *J* 4, CF_3), 70.4 (C-3), 69.1 (C-5), 42.6 (C-4), 39.3 (C-7), 32.2 (C-6). δ_F (400 MHz, $CDCl_3$) −62.39.

(–)-(*R*,*E*)-5-Hydroxy-1,7-diphenylhept-1-en-3-one 138



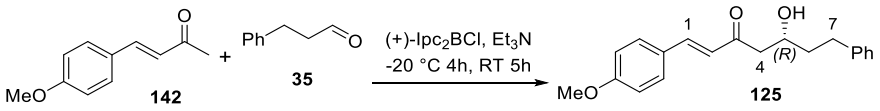
(+)-Ipc_2BCl (5 g, 15.59 mmol) was dissolved in Et_2O (100 mL) under nitrogen and cooled to 0 °C. Et_3N (5.9 mL, 42.51 mmol) and a solution of ketone **114** (2.7 g, 18.42 mmol) in Et_2O (100 mL) were added. The reaction mixture was stirred at this temperature for 2h, cooled to −78 °C and a solution of hydrocinnamaldehyde **35** in Et_2O (20 mL) was added dropwise. The temperature was increased to −30 °C and the reaction stirred overnight. The reaction mixture was allowed to warm to room temperature and stirred for 5 h, quenched with the addition of $NaHCO_3$ solution (200 mL) and the aqueous phase was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with saturated solution of brine (20 mL), dried over $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 5-30% EtOAc in hexane to give hydroxyketone **138** as a colourless oil (2.1 g, 53%, *er* 95.5).$[\alpha]_D^{21}$ −27 (*c*. 3.0 $CHCl_3$): δ_H (400 MHz, $CDCl_3$) 7.58 – 7.54 (3H, m, 1-H, Ar), 7.42 – 7.40 (3H. m, Ar), 7.31 – 7.17 (5H, m, Ar), 6.72 (1H, d, *J* 16, 2-H), 4.17 (1H, m, 5-H), 3.32 (1H, d, *J* 3, OH), 2.91 – 2.70 (4H, m, 4-H_2, 7-H_2), 1.95 – 1.87 (1H, m, 6-*H*H), 1.82 – 1.73 (1H, m, 6-H*H*); δ_C (100 MHz, $CDCl_3$) 200 (C=O), 143.6 (C-1), 141.9, 130.8, 129.0, 128.5, 128.4, 126.2 (C-2), 125.8, 67.5 (C-5), 46.8 (C-7), 38.1 (C-6), 31.8 (C-7).

(*E*)-4-(*p*-Methoxyphenyl)but-3-en-2-one 142



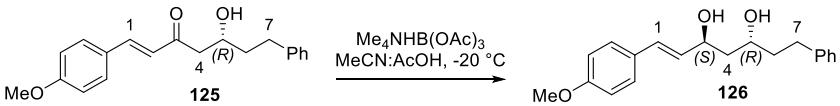
Anisaldehyde (1.22 mL, 10.0 mmol) was dissolved in acetone (7.4 mL, 0.1 mol) and water (2 ml) was added. The solution was cooled to 0 °C and a solution of 10% $NaOH_{(aq)}$ (5 mL) was added dropwise. After stirring at room temperature for 2 h, 2M HCl was added until neutralise the solution. The solid was filtered, washed with water and dried to give enone **142** as a white solid (1.58 g, 90%) mp 73-75; δ_H (400 MHz, $CDCl_3$) 7.49 (2H, d, *J* 9, Ar), 7.47 (1H, d, *J* 16, 1-H), 6.92 (2H, d, *J* 9, Ar), 6.61 (2H, d, *J* 16, 2-H), 3.84 (3H, s, OCH_3), 2.36 (3H, s, 4-H_3); δ_C (100 MHz, $CDCl_3$) 198.5 (CO), 161.7, 143.3 (C-1), 130.0, 127.16, 125.1 (C-2), 114.5, 55.5 (OCH_3), 27.5 (CH_3) Spectroscopic data in accord with the literature.[118]

(-)-(*R,E*)-5-Hydroxy-1-(4-methoxyphenyl)-7-phenylhept-1-en-3-one 125



(+)-Ipc_2BCl (2.31 g, 7.20 mmol) was dissolved in anhydrous Et_2O (80 mL) and cooled to 0 °C under nitrogen. Et_3N (2.70 mL, 19.73 mmol) and a solution of enone **142** (1.5 g, 8.51 mmol) in Et_2O (80 mL) were added. The reaction mixture was stirred for 2.5 h and cooled to −78 °C and a solution of dihydrocinnamaldehyde **35** (0.86 mL, 6.55 mmol) in Et_2O (15 mL) was added dropwise. The temperature was increased to −20 °C and the reaction stirred overnight. The reaction mixture was allowed to warm to room temperature and stirred for 4 h, quenched with the addition of $NaHCO_3$ solution (135 mL). The aqueous phase was extracted with Et_2O (3 × 200 mL) and the combined organic layers were dried over $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 5-30% EtOAc in hexane to give hydroxyketone **125** as a white solid (0.59 g, 30%, *er* 96:4). mp 61-63 °C; $[\alpha]_D^{22}$−45.0 (*c.* 1.0 $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3447, 3025, 2936, 2839, 1629, 1596; δ_H (400 MHz, $CDCl_3$) 7.52 (1H, d, *J* 16, 1-H), 7.52 – 7.48 (2H, m, Ar), 7.31 – 7.17 (5H, m, Ar), 6.94 – 6.90 (2H, m, Ar), 6.60 (1H, d, *J* 16, 2-H), 4.15 (1H, m, 5-H), 3.85 (3H, s, OCH_3), 2.90 – 2.83 (2H, m, 4-*H*H, 7-*H*H), 2.79 – 2.70 (2H, m, 4-H*H*, 7-H*H*), 1.90 (1H, m, 6-*H*H), 1.77 (1H, m, 6-H*H*); δ_C (100 MHz, $CDCl_3$) 201.0 (CO), 162.0, 143.6 (C-1), 142.1, 130.3, 128.6, 128.5, 126.9, 126.0, 124.2 (C-2), 114.6, 67.4 (C-5), 55.6 (OCH_3), 46.7 (C-7), 38.3 (C-6), 32.0 (C-4); Found (ESI) 311.1638 [MNa^+] ($C_{20}H_{22}O_3$ requires 311.1642).

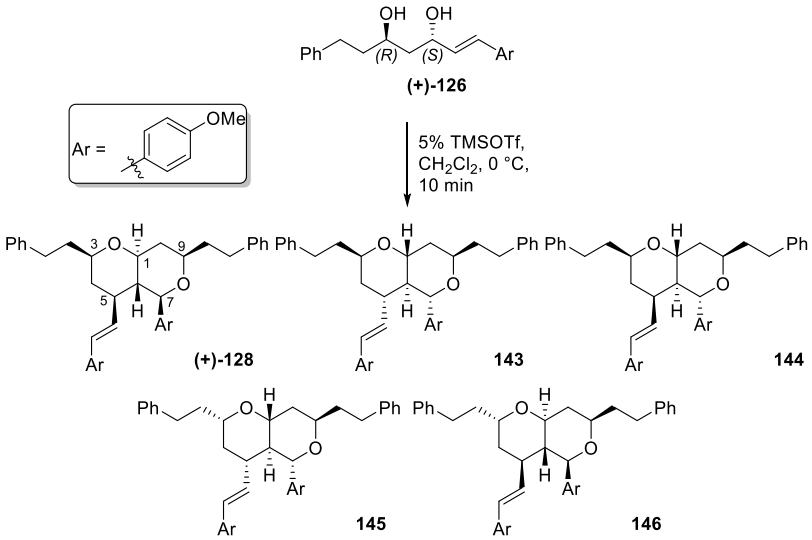
(+)-(3*S*, 5*R*, *E*)-1-(4-Methoxyphenyl)-7-phenylhept-1-ene-3,5-diol 126



$Me_4NHB(OAc)_3$ (3.06 g, 14.43 mmol) was dissolved in a 1:1 mixture of MeCN:AcOH (30 mL) under nitrogen and the solution was cooled to −40 °C. β-hydroxyketone **125** (0.56 g, 1.80 mmol) was dissolved in MeCN (2 mL) and added to the reaction mixture, which was warmed to −20 °C and stirred overnight. 0.5 N Rochelle's salt solution (15 mL) was added and the mixture diluted with CH_2Cl_2 (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed repeatedly with $NaHCO_{3(aq)}$. The organic phase was dried with $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 10-30%

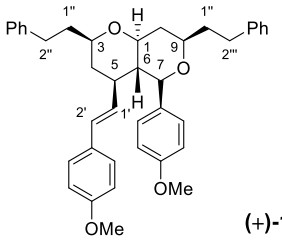
EtOAc in hexane to give *anti*-diol **126** as a light-yellow oil (0.46 g, 82%). $[\alpha]_D^{22}$+4.0 (*c.* 1.0 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.33 – 7.25 (4H, m, Ar), 7.22 – 7.16 (3H, m, Ar), 6.86 (2H, d, *J* 9 Ar), 6.56 (1H, d, *J* 16, 1-H), 6.14 (1H, dd, *J* 16, 6, 2-H), 4.63 (1H, q, *J* 6, 3-H), 4.01 (1H, m, 5-H), 3.81 (3H, s, OCH_3), 2.81 (1H, m, 7-*H*H), 2.68 (1H, m, 7-H*H*), 2.51 (2H, s(br), 2×OH), 1.93 – 1.74 (4H, m, 4-H_2, 6-H_2); δ_C (100 MHz, $CDCl_3$) 159.5, 142.1, 129.9 (C-1), 129.7 (C-2), 129.5, 128.6, 128.5, 127.8, 126.0, 114.2, 71.0 (C-3), 69.0 (C-5), 55.5 (OCH_3), 42.9 (C-4), 39.3 (C-6), 32.3 (C-7). Found (ESI) [MNa^+] 335.1624 ($C_{20}H_{24}O_3Na$ requires 335.1618).

Treatment of diol (+)-126 with TMSOTf



Diol **(+)-126** (0.50 mg, 0.16 mmol) was dissolved in dry CH_2Cl_2 (0.5 mL) under nitrogen and the solution was cooled to 0 °C. TMSOTf (1.5 µL, 0.008 mmol) was added with microsyringe and the mixture was stirred at this temperature for 10 min. Water (0.5 mL) was added and the two phases separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The crude product was purified by HPLC using a Waters SunFire Prep silica column with a flow of 1 mL/min and a gradient of EtOAc with hexane starting from 2% for 4 min, 5% for 10 min, 8% for 10 min,15% for 10 min and 30% for 10 min isolating blepharocalyxin analogue **(+)-128** (6.5 mg, 14% yield), **143** (1.4 mg, 3% yield), **144** (2.2 mg, 5% yield), **145** (1.2 mg, 2.5% yield), **146** (1 mg, 2% yield).

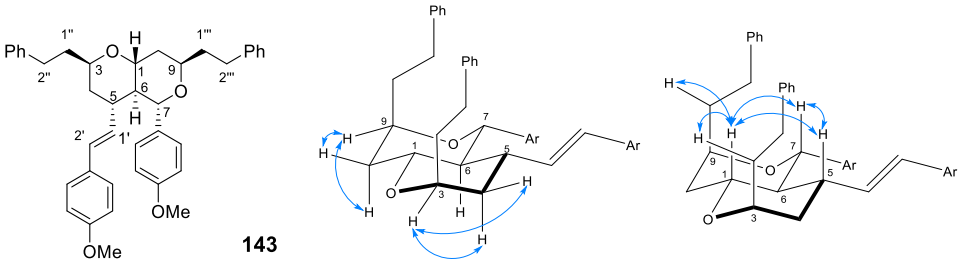
(+)-(1*S*, 3*R*, 5R, 6*R*, 7*R*, 9*R*)-3,9-di(phenethyl)-7-*p*-methoxyphenyl-5-(*E*)-(*p*-methoxyphen)ethenyl-2,8-dioxabicyclo[4.4.0]decane (+)-128



(+)-128

$[\alpha]_D^{23}$ +110.0 (*c*. 1.0, $CHCl_3$); All data in accordance with racemic product.

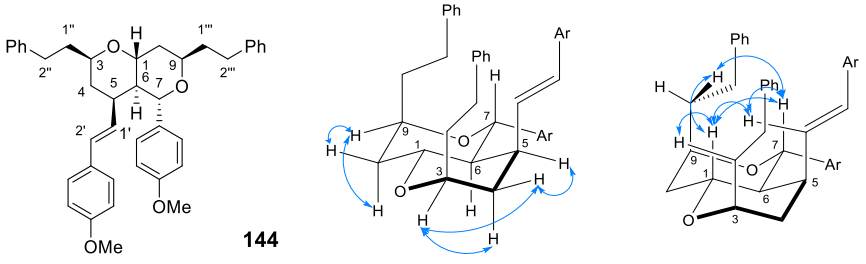
(1*R*, 3*R*, 5*S*, 6*S*, 7*S*, 9*R*)-3,9-di(phenethyl)-7-*p*-methoxyphenyl-5-(*E*)-(p-methoxy)phenethenyl-2,8-dioxabicyclo[4.4.0]decane 143



143

A colourless oil. ν_{max} (neat)/cm^{-1} 3026, 2927, 2856, 1607, 1511; δ_H (500 MHz, $CDCl_3$) 7.32 – 7.17 (12H, m, Ar), 6.72 – 6.66 (6H, m, Ar), 5.72 (1H, d, *J* 16, 2'-H), 5.01 (1H, dd, *J* 16, 9, 1'-H), 4.25 (1H, d, *J* 11, 7-H), 4.19 (1H, dt, *J* 11, 6, 9-H), 4.00 (1H, dt, *J* 11, 6, 3-H), 3.85 (1H, td, *J* 11, 4, 1-H), 3.77 (3H, m, OCH_3), 3.52 (3H, m OCH_3), 2.77 – 2.59 (4H, m, 2"-H_2, 2"'-H_2), 2.37 – 2.21 (3H, m, 1''-*H*H, 5-H, 1'''-*H*H), 2.01 (1H, td, *J* 12, 6, 10-*H*H), 1.85 – 1.70 (5H, m, 10-H*H*, 1''-H*H*, 1"'-H*H*, 4-*H*H, 6-H), 1.46 (1H, m, 4-H*H*); δ_C (125 MHz, $CDCl_3$) 159.1, 158.4, 142.0, 133.1, 132.0 (C-1'), 130.4, 129.7, 128.5, 128.4, 127.2 (C-2'), 126.8, 125.9, 113.8, 113.3, 75.7 (C-7), 72.9 (C-9), 72.0 (C-3), 66.7 (C-1), 55.3 (OCH_3), 55.0 (OCH_3), 51.5 (C-6), 37.5 (C-5), 37.0 (C-4), 35.6 (C-10), 33.6 (C-1'''), 32.8 (C-1''), 32.6, 32.4 (C-2"' & C-2''); Found (ESI) 611.3132 [MNa^+] ($C_{40}H_{44}O_4Na$ requires 611.3132).

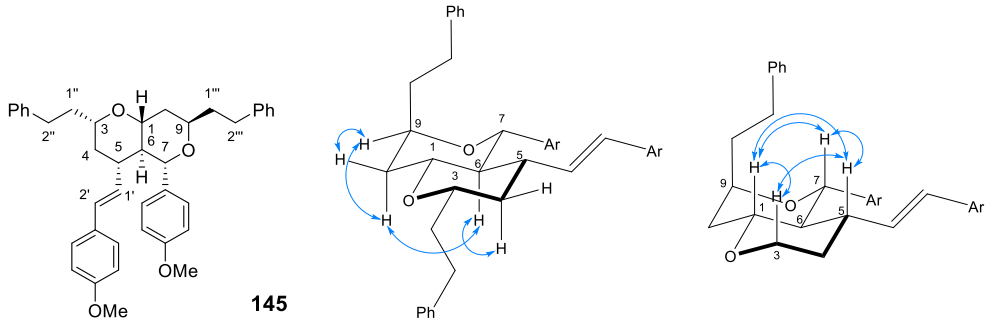
(1*R*, 3*R*, 5*R*, 6*S*, 7*S*, 9*R*)-3,9-di(phenethyl)-7-*p*-methoxyphenyl-5-(*E*)-(*p*-methoxy)phenethenyl-2,8-dioxabicyclo[4.4.0]decane 144



144

A colourless oil. ν_{max} (neat)/cm^{-1}: 3026, 2928, 2856, 1607, 1510; δ_H (500 MHz, $CDCl_3$) 7.28 – 7.21 (8H, m, Ar), 7.19 – 7.14 (6H, m, Ar), 6.89 – 6.85 (4H, m, Ar), 6.33 (1H, dd, *J* 16, 9, 1'-H), 6.02 (1H, d, *J* 16, 2'-H), 4.27 (1H, d, *J* 11, 7-H), 4.17 (2H, m, 9-H, 1-H), 3.94 (1H, m, 3-H), 3.84 (3H, m, OCH_3), 3.81 (3H, m, OCH_3), 2.74 – 2.67 (2H, m, 2''-*H*H, 2'''-*H*H), 2.65 – 2.57 (2H, m, 2"-H*H*, 2"'-H*H*), 2.26 – 2.19 (3H, m, 5-H, 1''-*H*H, 1'''-*H*H), 2.14 (1H, m, 4-*H*H), 2.00 – 1.75 (5H, m, 10-H_2, 6-H, 1''-H*H*, 1'''-H*H*), 1.58 (1H, m, 4-H*H*); δ_C (125 MHz, $CDCl_3$) 159.4, 159.1, 141.9, 131.8 (C-1'), 131.3, 130.2, 129.2, 128.5, 128.4, 128.3, 127.7 (C-2'), 127.2, 125.9, 125.8,114.1, 113.7, 73.4 (C-7), 73.1 (C-9), 71.6 (C-3), 62.7 (C-1), 55.4 (OCH_3), 55.3 (OCH_3), 48.7 (C-6), 36.12 (C-4 & C-1'''), 35.8 (C-10), 35.6 (C-5), 33.4 (C-1"), 32.9 (C-2"'), 32.5 (C2''); Found (ESI) 589.3292 [MH$^+$] ($C_{40}H_{45}O_4$ requires 589.3312).

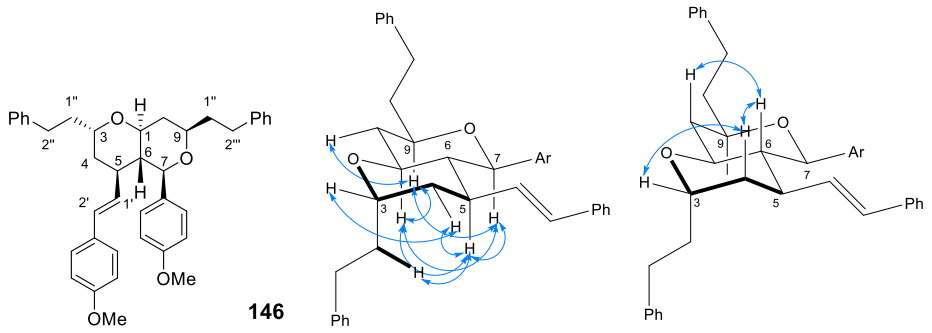
(1*R*, 3*S*, 5*S*, 6*S*, 7*S*, 9*R*)-3,9-di(phenethyl)-7-*p*-methoxyphenyl-5-((*E*)-*p*-methoxyphenethenyl)-2,8-dioxabicyclo[4.4.0]decane 145



145

A colourless oil. ν_{max} (neat)/cm^{-1}: 3026, 2931, 2856, 1607, 1511; δ_H (500 MHz, $CDCl_3$) 7.30 – 7.26 (4H, m, Ar), 7.20 – 7.16 (8H, m, Ar), 6.72 – 6.64 (6H, m, Ar), 5.74 (1H, d, *J* 16, 2'-H), 5.01 (1H, dd, *J* 16, 9, 1'-H), 4.23 (1H, d, *J* 10, 7-H), 4.19 (1H, m, 9-H), 3.76 (3H, m, OCH_3), 3.58 (1H, m, 1-H), 3.50 (3H, m OCH_3), 3.45 (1H, m, 3-H), 2.80 – 2.58 (4H, m, 2"-H_2, 2"'-H_2), 2.30 – 2.04 (3H, m, 10-*H*H, 5-H, 1''-*H*H), 1.96 (1H, m, 1''-H*H*), 1.89 – 1.79 (2H, m, 10-H*H*, 1'''-*H*H), 1.73 – 1.66 (2H, m, 1"'-H*H*, 6-H), 1.58 (1H, m, 4-*H*H), 1.32 (1H, m, 4-*H*H); δ_C (125 MHz, $CDCl_3$) 159.1, 158.4, 142.1, 142.0, 133.2, 132.1 (C-1'), 130.4, 129.6, 128.4, 128.4, 128.4, 128.3, 127.1 (C-2'), 126.8, 125.8, 125.7, 113.7, 113.3, 75.9 (C-7 & C-9), 75.2 (C-1), 72.8 (C-3), 55.2 (OCH_3), 54.9 (OCH_3), 51.1 (C-6), 42.3 (C-5), 40.2 (C-4), 37.7 (C-1'''), 35.4 (C-1"), 33.4 (C-10), 32.5 (C-2"'), 31.6 (C2''); Found (ESI) 589.3331 [MH$^+$] ($C_{40}H_{45}O_4$ requires 589.3312).

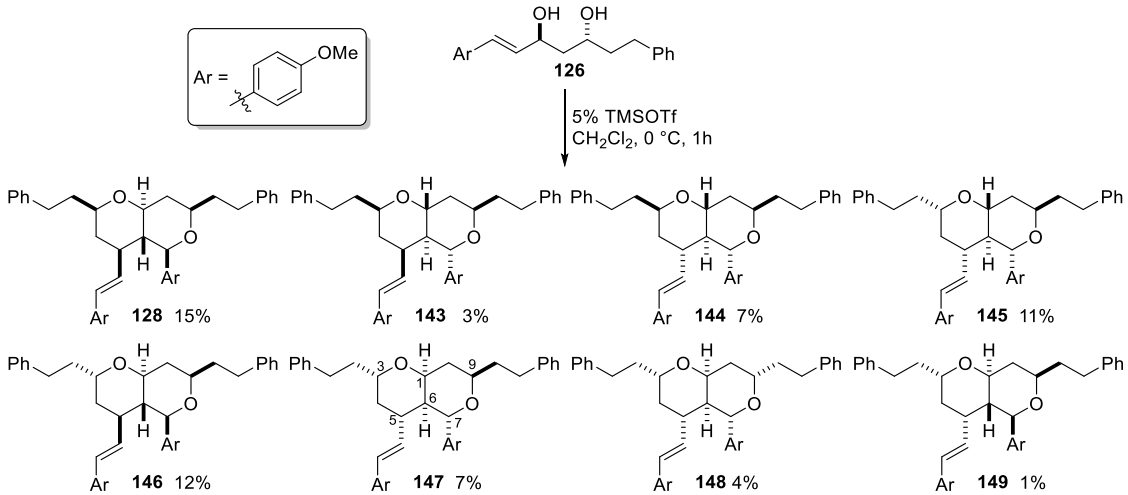
(1*S*, 3*S*, 5*R*, 6*R*, 7*R*, 9*R*)-3,9-di(phenethyl)-7-*p*-methoxyphenyl-5-((*E*)-*p*-methoxyphenethenyl)-2,8-dioxabicyclo[4.4.0]decane 146



146

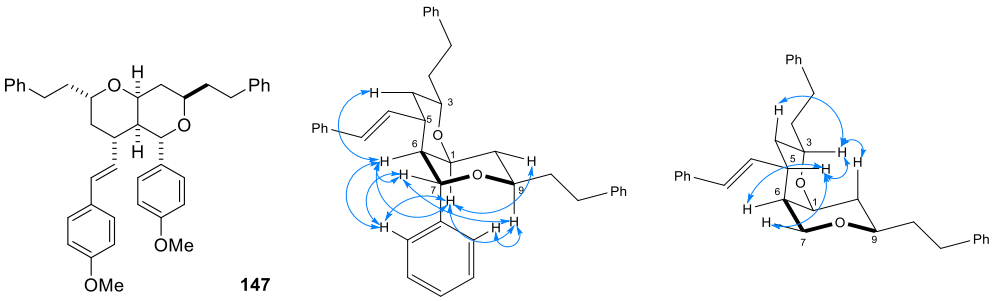
A colourless oil. ν_{max} (neat)/cm^{-1}: 3025, 2936, 2830, 1610, 1510; δ_H (500 MHz, $CDCl_3$) 7.32 – 7.24 (6H, m, Ar), 7.22 – 7.16 (6H, m, Ar), 6.73 – 6.64 (6H, m, Ar), 5.70 (1H, d, *J* 16, 2'-H), 4.99 (1H, dd, *J* 16, 9, 1'-H), 3.99 (1H, d, *J* 10, 7-H), 3.99 (1H, m, 3-H), 3.77 (3H, s, OCH_3), 3.61 (1H, m, 1-H), 3.54 (1H, m, 9-H), 3.51 (3H, m, OCH_3), 2.79 – 2.64 (4H, m, 2''-H_2, 2'''-H_2), 2.38 – 2.25 (2H, m, 5-H, 1''-*H*H), 1.99 – 1.89 (2H, m, 10-*H*H, 1'''-*H*H), 1.84 – 1.69 (3H, m, 4-*H*H, 1''-H*H*, 1'''-H*H*), 1.64 (1H, q, *J* 10, 6-H), 1.56 (1H, m, 10-H*H*), 1.43 (1H, m, 4-H*H*); δ_C (125 MHz, $CDCl_3$) 159.0, 158.4, 142.2, 142.1, 133.2, 132.2 (C-1'), 130.5, 129.7, 128.5, 128.5, 128.4, 128.3, 127.0 (C-2'), 126.8, 125.9, 125.7, 113.6, 113.4, 82.7 (C-7), 75.0 (C-9), 71.8 (C-3), 70.6 (C-1), 55.3 (OCH_3), 54.9 (OCH_3), 51.5 (C-6), 38.3 (C-10), 37.5 (C-1'''), 37.2 (C-5), 37.2 (C-4), 32.7 (C-1''), 32.3, 31.4 (C-2'' & C-2'''). Found (ESI) 589.3309 [MH$^+$] ($C_{40}H_{44}O_4$ requires 589.3312).

Treatment of racemic diol 126 with TMSOTf



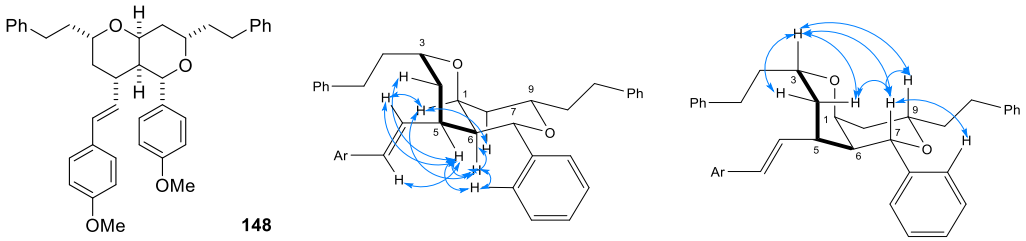
Diol **126** (0.40 mg, 1.28 mmol) was dissolved in CH_2Cl_2 (2.5 mL) under nitrogen and the solution was cooled to 0 °C. TMSOTf (12 µL, 0.064 mmol) was added and the mixture was stirred at this temperature for 1 h. Water (3 mL) was added and the two phases separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. . The crude product was purified by HPLC using a Waters SunFire Prep silica column with a flow of 1 mL/min and a gradient of EtOAc with hexane starting from 2% for 4 min, 5% for 10 min, 8% for 10 min,15% for 10 min and 30% for 10 min isolating blepharocalyxin analogue **128** (44.6 mg, 15% yield), **143** (13 mg, 3% yield), **144** (26 mg, 7% yield), **145** (42 mg, 11% yield), **146** (44 mg, 12% yield), **147** (26 mg, 7% yield), **148** (16 mg, 4% yield), **149** (12 mg, 1% yield).

(1*S,3*S**,5*S**,6*S**,7*S**,9*R**)-3,9-di(phenethyl)-7-*p*-methoxyphenyl-5-((*E*)-*p*-methoxyphenethenyl)-2,8-dioxabicyclo[4.4.0]decane 147**



A colourless. ν_{max} (neat)/cm^{-1} 3024, 2918, 2851, 1607, 1509; δ_H (500 MHz, $CDCl_3$) 7.40 – 7.36 (2H, m, Ar), 7.30 – 7.25 (7H, m, Ar), 7.21 – 7.16 (5H, m, Ar), 6.89 – 6.86 (2H, m, Ar), 6.83 – 6.80 (2H, m, Ar), 6.52 (1H, d, *J* 16, 2'-H), 5.82 (1H, dd, *J* 16, 9, 1'-H), 5.15 (1H, s, 7-H), 4.32 (1H, m, 1-H), 3.81 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.73 (1H, m, 3-H), 3.40 (1H, m, 9-H), 2.97 – 2.86 (2H, m, 5-H, 2''-*H*H), 2.79 (1H, m, 2'''-*H*H), 2.68 (1H, m, 2'''-H*H*), 2.59 (1H, m, 2''-H*H*), 2.37 (1H, dd, *J* 11, 5, 6-H), 2.08 (1H, q, *J* 12, 10-*H*H), 1.94 (1H, m, 1'''-*H*H), 1.88-1.69 (4H, m, 1''-H_2, 4-*H*H, 1'''-H*H*), 1.52 (1H, m, 10-H*H*), 1.42 (1H, q, *J* 12, 4-H*H*); δ_C (100 MHz, $CDCl_3$) 158.9, 158.6, 142.2, 142.2, 132.2, 131.2 (C-2'), 130.6 (C-1'), 130.0, 128.6, 128.4, 128.3, 128.3, 128.2, 127.3, 125.8, 125.7, 113.9, 113.8, 74.4 (C-7), 69.4 (C-1), 69.1 (C-9), 67.4 (C-3), 55.3 (2×OCH_3), 40.1 (C-6), 39.2 (C-4), 38.2 (C-1'' & C-1'''), 37.1 (C-5), 32.0 (C-2''), 31.9 (C-10), 31.7 (C-2'''); Found (ESI) 611.3168 [MNa^+] ($C_{40}H_{44}O_4Na$ requires 611.3132).

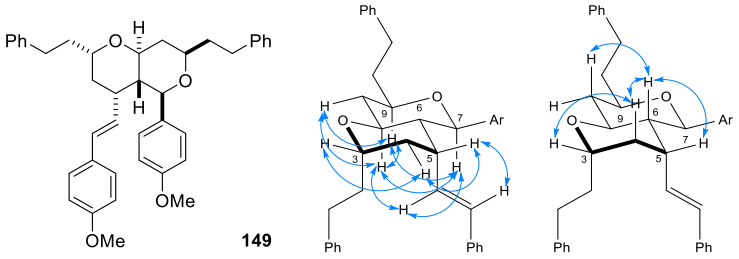
(1*S,3*S**,5*S**,6*S**,7*S**,9*S**)-3,9-di(phenethyl)-7-*p*-methoxyphenyl-5-((*E*)-*p*-methoxyphenethenyl)-2,8-dioxabicyclo[4.4.0]decane 148**



148

A colourless oil. ν_{max} (neat)/cm^{-1} 3026, 2925, 2857, 1608, 1511; δ_H (500 MHz, $CDCl_3$) 7.32 – 7.29 (2H, m, Ar), 7.29 – 7.24 (5H, m, Ar), 7.20 – 7.16 (5H, m, Ar), 7.05 – 7.02 (2H, m, Ar), 6.88 – 6.85 (2H, m, Ar), 6.79 – 6.76 (2H, m, Ar), 5.74 (1H, d, *J* 16, 2'-H), 5.66 (1H, dd, *J* 16, 7, 1'-H), 4.50 (1H, d, *J* 11, 7-H), 4.23 (1H, q, *J* 3, 1-H), 3.96-3.87 (2H, m, 3-H, 9-H), 3.77 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 2.79 – 2.73 (2H, m, 2''-*H*H, 2'''-*H*H), 2.71 – 2.63 (2H, m, 2''-H*H*, 2'''-H*H*), 2.10 – 2.01 (2H, m, 5-H, 10-*H*H), 1.90 – 1.83 (3H, m, 6-H, 1''-*H*H, 1'''-*H*H), 1.81 – 1.72 (3H, m, 4-*H*H, 1''-H*H*, 1'''-H*H*), 1.67 (1H, m, 10-H*H*), 1.59 (1H, m, 4-H*H*); δ_C (125 MHz, $CDCl_3$) 159.3, 158.7, 142.5, 142.2, 133.1, 132.0 (C-2'), 130.3, 129.4, 128.5, 128.5, 128.3, 128.2, 127.6 (C-1'), 127.0, 125.7, 125.6, 113.8, 113.7, 80.12 (C-7), 72.6, 71.9 (C-3 & C-9), 63.6 (C-1), 55.3 (2×OCH_3), 45.3 (C-6), 37.7, 37.1 (C-1'' & C-1'''), 37.0 (C-10), 36.0 (C-5), 32.0, 31.6 (C-2'' & C-2'''), 31.2 (C-4); Found (ESI) 611.3113 [MNa^+] ($C_{40}H_{44}O_4Na$ requires 611.3132).

(1*S,3*S**,5*S**,6*R**,7*R**,9*R**)-3,9-di(phenethyl)-7-*p*-methoxyphenyl-5-((*E*)-*p*-methoxyphenethenyl)-2,8-dioxabicyclo[4.4.0]decane 149**

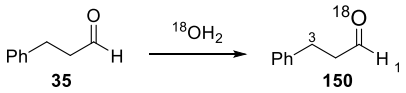


149

A colourless oil. ν_{max} (neat)/cm^{-1} 3026, 2925, 2853, 1609, 1511; δ_H (500 MHz, $CDCl_3$) 7.27 – 7.21 (8H, m, Ar), 7.18 – 7.15 (6H, m, Ar), 6.89 – 6.84 (4H, m, Ar), 6.33 (1H, dd, *J* 16, 10, 1'-H), 5.99 (1H, d, *J* 16, 2'-H), 4.01 (1H, d, *J* 10.5, 7-H), 3.98 – 3.92 (2H, m, 1-H, 3-H), 3.83 (3H, s, OCH_3), 3.81 (3H, m, OCH_3), 3.49 (1H, m, 9-H), 2.75 – 2.59 (4H, m, 2''H_2, 2'''H_2), 2.29 – 2.20 (2H, m, 5-H, 1'''-*H*H), 2.14 (1H, m, 10-*H*H), 1.99 – 1.92 (2H, m, 4-*H*H, 1''-*H*H), 1.86 – 1.76 (3H, m, 6-H, 1''-H*H*, 1'''-H*H*), 1.59 – 1.50 (2H, m, 10-H*H*, 4-H*H*); δ_C (100 MHz, $CDCl_3$) 159.3, 159.1, 142.1, 142.0, 131.6 (C-2'), 131.5, 130.2, 129.2, 128.5, 128.3, 128.3, 128.0 (C-1'), 127.2, 125.8, 125.7, 114.1, 113.5, 80.5 (C-

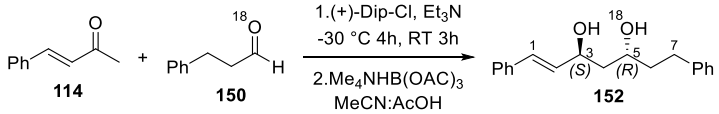
7), 74.8 (C-9), 71.7 (C-3), 66.4 (C-1), 55.4 (OCH_3), 55.3 (OCH_3), 48.5 (C-6), 38.6 (C-4), 37.5 (C-1''), 36.3 (C-10), 36.1 (C-1'''), 35.5 (C-5), 32.9, 31.4 (C-2'' and C-2'''); Found (ESI) 611.3167 [MNa^+] ($C_{40}H_{44}O_4Na$ requires 611.3132).

[^{18}O]-Dihydrocinnamaldehyde 150



Dihydrocinnamaldehyde **35** (1 g, 7.45 mmol) was dissolved in d_3-acetonitrile (0.8 mL) and water-^{18}O (0.15 mL, 8.20 mmol) was added. The reaction mixture was stirred for 2 h and diluted with CH_2Cl_2 (10 mL). The solution was dried over $MgSO_4$ and the solvent removed *in vacuo* to give aldehyde **150** as a colourless oil in quantitative yield. δ_H (400 MHz, CD_3CN) 9.73 (1H, s, 1-H), 7.31–7.18 (5H, m, Ar), 2.91 (2H, t, *J* 7.5, 3-H_2). 2.74 (2H, t, *J* 7.5, 2-H_2); δ_C (100 MHz, CD_3CN) 203.14 ($C^{16}OH$), 203.09 ($C^{18}OH$), 141.9, 129.4, 129.2, 127.0, 45.6 (C-2), 28.6 (C-3).

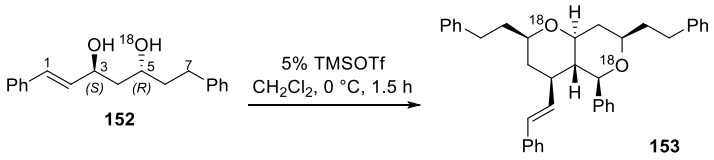
[5-^{18}O]-(+)-(1*E*, 3*S*, 5*R*)-1,7-Diphenylhept-1-ene-3,5-diol 152



Benzylacetone **114** (0.80 g, 5.51 mmol) was dissolved in Et_2O (50 mL) and cooled to 0 °C under nitrogen. Et_3N (1.54 mL, 11.01 mmol) and a solution of (+)-Ipc_2BCl (4 mL, 1.2 M, 4.77 mmol) were added dropwise and stirred for 2 h. The reaction mixture was cooled to −78 °C and a solution of label [^{18}O]-dihydrocinnamaldehyde **150** in THF (2.5 mL) was added dropwise. The temperature was increased to −30 °C and the reaction stirred overnight. The reaction mixture was allowed to warm to room temperature and stirred for 3 h, quenched with the addition of $NaHCO_3$ solution (50 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by column chromatography using 5-30% EtOAc in hexane to give the corresponding β-hydroxyketone in 96:4 *er*. $Me_4NHB(OAc)_3$ (2.03 g, 7.70 mmol) was dissolved in a 1:1 mixture of MeCN:AcOH (8 mL) and stirred for 30 min. The solution was cooled to −20 °C and a solution of hydroxyketone (0.27 g, 0.96 mmol) in MeCN (2.0 mL) was added to the reaction mixture and stirred overnight. Semi-saturated Rochelle's salt solution (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed repeatedly with $NaHCO_{3(aq)}$. The organic phase was dried with $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 10-20% EtOAc in hexane to

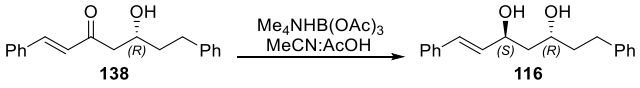
give [5-^{18}O]-diol **152** as a colourless oil (0.17 g, 17% over two steps, *dr* 88:12). $[\alpha]_D^{22}$ +5.0 (*c*. 1.0 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.38–7.17 (10H, m, Ar), 6.63 (1H, m, *J* 16, 1-H), 6.28 (1H, dd, *J* 16, 6, 2-H), 4.67 (1H, m, 3-H), 4.03 (1H, m, 5-H), 2.80 (1H, m, 7-H*H*), 2.69 (1H, m, 7-H*H*), 2.47 (1H, s(br), OH), 2.36 (1H, s(br), OH), 1.93–1.75 (4H, m, 4-H_2, 6-H_2); δ_C (100 MHz, $CDCl_3$) 142.0, 136.7, 132.0 (C-2), 130.2 (C-1), 128.7, 128.6, 128.5, 127.9, 126.6, 126.1, 70.8 (C-3), 69.07 (C-^{16}OH), 68.04 (C-^{18}OH), 42.8 (C-4), 39.4 (C-6), 32.3 (C-7).

[^{18}O]-(1*R*,3*S*,5*S*,6*S*,7*S*,9*S*)-3,9-diphenylethyl-7-phenyl-5-(*E*)-phenethenyl-2,8-dioxabicyclo[4.4.0]decane 153



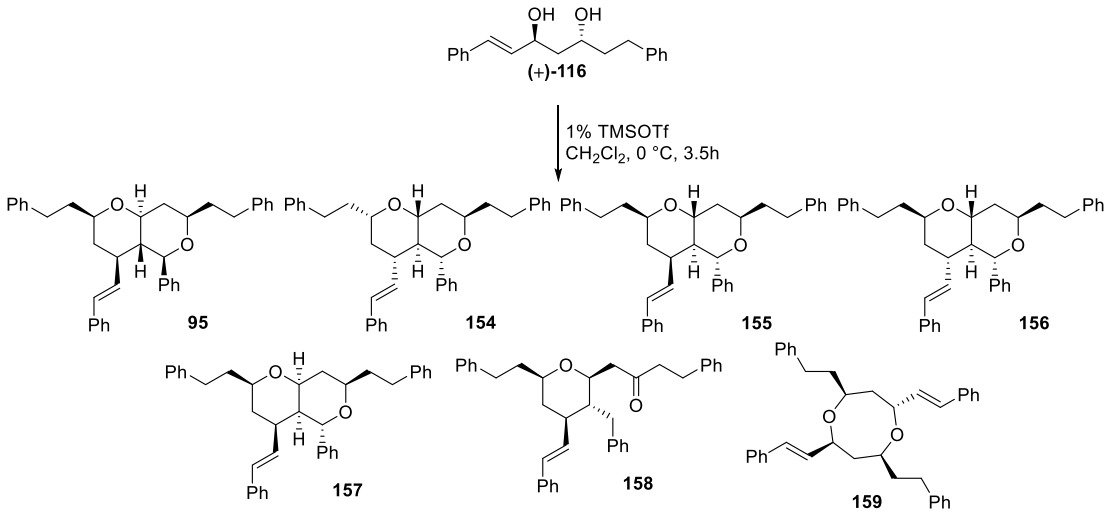
Diol **152** (0.10 mg, 0.35 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) under nitrogen and the solution was cooled to 0 °C. TMSOTf (3.2 µL, 0.018 mmol) was added by microsyringe and the mixture was stirred at this temperature for 1.5 h. Water (1 mL) was added and the two phases separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The crude product was purified by column chromatography. Elution with 2.5% EtOAc in petroleum ether 40-60 °C gave blepharocalyxin analogue **[^{18}O]-153** as a colourless oil (7.8 mg, 8% yield). δ_H (400 MHz, $CDCl_3$) 7.30–7.25 (4H, m, Ar), 7.20–7.15 (6H, m, Ar), 7.12–7.05 (2H, m, Ar), 6.98 (1H, m, Ar), 6.72 (2H, m, Ar), 5.81 (1H, d, *J* 16, 2'-H), 5.14 (1H, dd, *J* 16, 9, 1'-H), 4.01 (1H, d, *J* 10, 7-H), 3.55 (1H, m, 9-H), 3.45 (1H, m, 3-H), 3.37 (1H, m, 1-H), 2.81–2.67 (4H, m, 2"-H_2, 2"'-H_2), 2.19 (1H, m, 5-H), 2.07 (1H, m, 10-*H*H), 1.97 (1H, m, 1"'-*H*H) 1.91–1.78 (2H, m, 1"'-H*H*, 1"-*H*H), 1.73–1.63 (6H, m, 6-H, 10-H*H*, 1"- H*H*), 1.55 (1H, m, 4-*H*H), 1.33 (1H, m, 4-H*H*); δ_C (100 MHz, $CDCl_3$) 142.1, 141.0, 137.4, 134.1 (C-1'), 128.5, 128.5, 128.3 (C-2'), 128.3, 128.2, 128.0, 127.9, 127.8, 126.5, 125.8, 125.7, 125.7, 83.39 & 83.37 (C-7), 79.13 & 79.11 (C-1), 75.77 & 75.74 (C-9), 75.02 & 75.00 (C-3), 50.6 (C-6), 41.9 (C-5), 40.3 (C-4), 38.1 (C-10), 37.6, 37. 5 (C-1" & C-1"'), 31.6, 31.3 (C-2" & C-2"'). Found (ESI) 551.2939 [MNa^+] ($C_{38}H_{40}O_2$ requires 551.2921 & Found (ESI) 555.3005 [MNa^+] ($C_{38}H_{40}{}^{18}O_2$ requires 555.3021).

(+)-(3*S*, 5*R*, *E*)-1,7-Diphenylhept-1-ene-3,5-diol 116



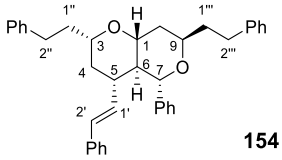
$Me_4NHB(OAc)_3$ (3.63 g, 17.12 mmol) was dissolved in a 1:1 mixture of MeCN:AcOH (36 mL) under nitrogen and the solution cooled to −40 °C. Hydroxyketone **138** (0.6 g, 2.14 mmol) was dissolved in MeCN (2.5 mL) and added to the reaction mixture, which was allowed to warm to −20 °C and stirred overnight. Rochelle's salt solution 0.5 N (30 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed repeatedly with $NaHCO_{3(aq)}$. The organic phase was dried with $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 2-30% EtOAc in hexane to give diol **(+)-116** as a white solid (0.51 g, 84%). mp 75-77; $[\alpha]_D^{23}$ +5.0 (*c*. 3.0 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.39 – 7.16 (10H, m, Ar), 6.63 (1H, m, *J* 16, 1-H), 6.28 (1H, dd, *J* 16 6, 2-H), 4.67 (1H, m, 3-H), 4.03 (1H, m, 5-H), 2.84 – 2.65 (1H, m, 7-HH), 2.73 – 2.65 (1H, m, 7-HH), 2.45 (1H, d, *J* 4, OH), 2.34 (1H, d, *J* 4 OH), 1.94 – 1.75 (4H, m, 4-H_2, 6-H_2); δ_C (100 MHz, $CDCl_3$) 141.9 , 136.6 , 131.8 (C-2), 130.1 (C-1), 128.6, 128.5, 128.4, 127.7, 126.5, 125.9, 70.7 (C-3), 68.9 (C-5), 42.7 (C-4), 39.2 (C-6), 32.1 (C-7).

Treatment of diol (+)-116 with TMSOTf



Diol **(+)-116** (0.40 mg, 1.46 mmol) was dissolved in CH_2Cl_2 (3 mL) under nitrogen and the solution was cooled to 0 °C. TMSOTf (13 µL, 0.073 mmol) was added and the mixture was stirred at this temperature for 1.5 h. Water (3 mL) was added and the two phases separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The crude product was purified by HPLC using Waters SunFire Prep silica column with a flow of 1 mL/min and a gradient of EtOAc with hexane isolating blepharocalyxin analogue **95** (79 mg, 20% yield), **154** (20 mg, 5% yield), **155** (10 mg, 2.5% yield), **156** (10 mg, 2.5% yield), **157** (20.5 mg, 5% yield), tetrahydropyran **158** (19.2 mg, 7% yield), 1,5-dioxocane **159** (21.1 mg, 5% yield).

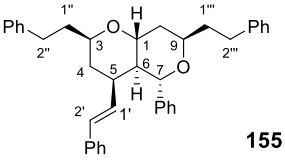
(1*R*,3*S*,5*S*,6*S*,7*S*,9*R*)-3,9-phenylethyl-7-phenyl-5-(*E*)-phenethenyl-2,8-dioxabicyclo[4.4.0]decane 154



154

A colourless oil. ν_{max} (neat)/cm^{-1} 3025, 2926, 2853, 1495; δ_H (500 MHz, $CDCl_3$) 7.31 – 7.26 (7H, m, Ar), 7.21 – 7.15 (9H, m, Ar), 7.13 – 7.08 (3H, m, Ar), 7.03 – 6.99 (1H, m, Ar), 6.72 (2H, d, *J* 9, Ar), 5.85 (1H, d, *J* 16, 2'-H), 5.18 (1H, dd, *J* 16, 9, 1'-H), 4.30 (1H, d, *J* 10, 7-H), 4.23 (1H, m, 9-H), 3.62 (1H, td, *J* 11, 4.5, 1-H), 3.49 (1H, m, 3-H), 2.82 – 2.60 (4H, m, 2''-H_2, 2'''-H_2), 2.32 – 2.19 (2H, m, 1'''-*H*H, 5-H), 2.11 (1H, td, *J* 12, 6, 10-*H*H), 1.99 (1H, dd, 13, 4.5, 10H*H*), 1.94 – 1.67 (4H, m, 1'''-H*H*, 1''H_2, 6-H), 1.58 (1H, m, 4-*H*H), 1.36 (1H, q, *J* 12, 4-H*H*); δ_C (125 MHz, $CDCl_3$) 142.2, 142.1, 141.0, 137.45, 134.1 (C-1'), 128.7, 128.6, 128.5, 128.4, 128.4 (C-2'), 128.2, 128.1, 128.0, 126.64, 126.0, 125.9, 125.8, 76.6 (C-7), 76.0 (C-3), 75.2 (C-1), 73.0 (C-9), 50.7 (C-6), 42.5 (C-5), 40.2 (C-4), 37.7 (C-1''), 35.4 (C-10), 33.5 (C-1'''), 32.6 (C-2'''), 31.7 (C2''); Found (ESI) 551.2922 [MNa$^+$] ($C_{38}H_{40}O_2Na$ requires 551.2921).

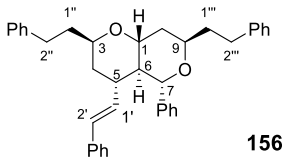
(1*R*,3*R*,5*R*,6*S*,7*S*,9*R*)-3,9-phenylethyl-7-phenyl-5-(*E*)-phenethenyl-2,8-dioxabicyclo[4.4.0]decane 155



155

A colourless oil. δ_H (500 MHz, $CDCl_3$) 7.37 – 7.22 (14H, m, Ar), 7.19 – 7.13 (6H, m, Ar), 6.50 (1H, dd, *J* 16, 10, 1'-H), 6.09 (1H, d, *J* 16, 2'-H), 4.32 (1H, d, *J* 10, 7-H), 4.20 (2H, m, 9-H, 1-H), 3.95 (1H, m, 3-H), 2.75 – 2.67 (2H, m, 2''-*H*H, 2'''-*H*H), 2.65 – 2.58 (2H, m, 2''-H*H*, 2'''-H*H*), 2.30 – 2.20 (3H, m, 5-H, 1''-*H*H, 1'''-*H*H), 2.15 (1H, m, 4-*H*H), 2.03 – 1.92 (2H, m, 10-*H*H, 6-H), 1.90 – 1.77 (3H, m, 10-H*H*, 1''-H*H*, 1'''-H*H*) 1.59 (1H, m, 4-H*H*); δ_C (125 MHz, $CDCl_3$) 141.9, 139.1, 137.3, 132.6 (C-2'), 129.9 (C-1'), 128.7, 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 127.4, 126.1, 125.9, 125.8, 73.9 (C-7), 73.2 (C-9), 71.6 (C-3), 62.6 (C-1), 48.7 (C-6), 36.14 (C-4 & C-1''), 35.8 (C-10), 35.5 (C-5), 33.4 (C-1'''), 32.9 (C-2'''), 32.4 (C2'')

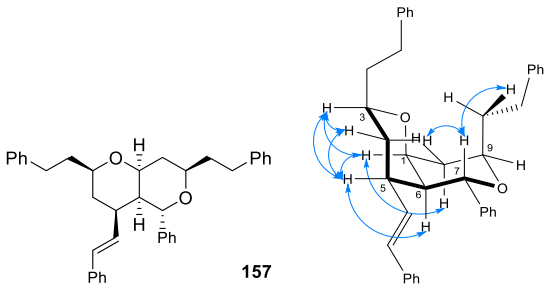
(1*R*,3*R*,5*S*,6*S*,7*S*,9*R*)-3,9-phenylethyl-7-phenyl-5-(*E*)-phenethenyl-2,8-dioxabicyclo[4.4.0]decane 156



156

A colourless oil. ν_{max} (neat)/cm^{-1} 3025, 2930, 2859, 1733, 1602, 1495; δ_H (500 MHz, $CDCl_3$) 7.32 – 7.15 (15H, m, Ar), 7.12 – 7.07 (2H, m, Ar), 7.02 (1H, m, Ar), 6.73 – 6.70 (2H, m, Ar), 5.81 (1H, d, *J* 16, 2'-H), 5.16 (1H, dd, *J* 16, 10, 1'-H), 4.30 (1H, d, *J* 10, 7-H), 4.20 (1H, m, 9-H), 4.00 (1H, m, 3-H), 3.87 (1H, m, 1-H), 2.79 – 2.57 (4H, m, 2''-H_2, 2'''-H_2), 2.43 – 2.20 (3H, m, 5-H, 1'''-*H*H, 1''-*H*H), 2.02 (1H, m, 10-*H*H), 1.88–1.72 (5H, m, 6-H, 10-H*H*, 1'''-*H*H, 1''-*H*H, 4-HH), 1.47 (2H, m, 4-H*H*); δ_C (125 MHz, $CDCl_3$) 142.0, 142.0, 140.8, 137.3, 134.0 (C-1'), 128.6, 128.5, 128.4, 128.2 (C-2'), 128.0, 127.8, 126.6, 125.9, 125.8, 76.4 (C-7), 72.9 (C-9), 71.9 (C-3), 66.6 (C-1), 51.0 (C-6), 37.6 (C-5), 36.9 (C-4), 35.6 (C-10), 33.6 (C-1'''), 32.9 (C-1''), 32.5, 32.4 (C-2''' and C-2''); Found (ESI) 551.2910 [MNa$^+$] ($C_{38}H_{40}O_2Na$ requires 551.2921).

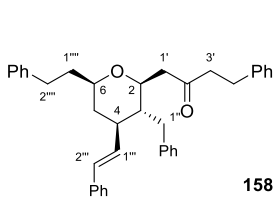
(1*R*,3*R*,5*R*,6*S*,7*S*,9*R*)-3,9-phenylethyl-7-phenyl-5-(*E*)-phenethenyl-2,8-dioxabicyclo[4.4.0]decane 157



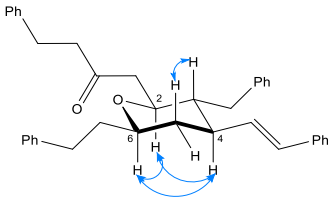
157

ν_{max} (neat)/cm^{-1} 3025, 2918, 2851, 1601, 1494; δ_H (500 MHz, $CDCl_3$) 7.37 – 7.35 (2H, m, Ar), 7.33 – 7.26 (6H, m, Ar), 7.24 – 7.18 (7H, m, Ar), 7.14 – 7.10 (3H, m, Ar), 6.70 – 6.68 (2H, m, Ar), 5.99 (1H, d, *J* 16, 2'-H), 5.21 (1H, dd, *J* 16, 8, 1'-H), 5.02 (1H, d, *J* 11, 7-H), 4.02 (1H, q, *J* 7, 9-H), 3.90 (1H, s, 1-H), 3.47 (1H, m, 3-H), 2.90 (1H, m, 2''-*H*H), 2.82 – 2.62 (3H, m, 2''-H*H*, 2'''-H_2), 2.57 – 2.50 (2H, m, 5-H, 1'''-*H*H), 2.25 – 2.12 (3H, m, 6-H, 1'''-H*H*, 10-*H*H), 2.03 – 1.96 (2H, m, 10-H*H*, 1''-*H*H), 1.88 (1H, m, 1''-H*H*), 1.61 – 1.50 (2H, m, 4-H_2); δ_C (125 MHz, $CDCl_3$) 142.6, 142.3, 141.9, 137.3, 133.9 (C-1'), 128.7, 128.5, 128.4, 128.3, 128.3, 128.0, 127.9, 127.3 (C-2'), 126.3, 126.0, 125.7, 125.6, 76.6 (C-3), 75.2 (C-1), 71.8 (C-9), 69.8 (C-7), 44.3 (C-6), 43.7 (C-5), 38.2 (C-1''), 34.9 (C-1'''), 34.1 (C-10), 32.9 (C-2'''), 32.8 (C-4), 31.7 (C-2''); Found (ESI) 551.2907 [MNa$^+$] ($C_{38}H_{40}O_2Na$ requires 551.2921).

1-(2S,3R,4R,6R)-2-(4'-phenylbutan-2'-one)-3-benzyl-4-(E)-phenethenyl-6-phenylethyl-tetrahydropyran 158

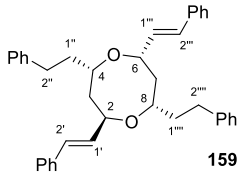


158

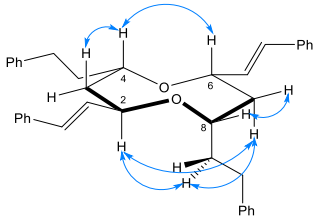


A colourless oil. ν_{max} (neat)/cm^{-1} 3025, 2925, 2852, 1713, 1495,; δ_H (500 MHz, $CDCl_3$) 7.30 – 7.10 (20H, m, Ar), 6.43 (1H, d, *J* 16, 2'''-H), 6.00 (1H, dd, *J* 16, 9, 1'''-H), 3.74 (1H, td, *J* 10, 3, 2-H), 3.31 (1H, m, 6-H), 2.92 – 2.76 (4H, m, 4'-H_2, 1''-*H*H, 3'-*H*H), 2.72 – 2.52 (4H, m, 3'-H*H*, 2''''-H_2, 1'-*H*H), 2.48 – 2.43 (2H, m, 1'-H*H*, 1''-H*H*), 2.26 (1H, m, 4-H), 1.75 (1H, m, 1''''-*H*H), 1.70 – 1.60 (3H, m, 1''''-H*H*, 3-H*H*, 5-*H*H), 1.34 (1H, m, 5-H*H*); δ_C (125 MHz, $CDCl_3$) 209.0 (CO), 142.1, 141.2, 140.5, 137.2, 133.6 (C-2'''), 131.2 (C-1'''), 129.1, 128.5, 128.4, 128.4, 128.3, 128.3, 127.2, 126.1, 126.0, 125.7, 78.53 (C-2), 75.3 (C-6), 47.6 (C-1'), 46.0 (C-4'), 46.0 (C-3), 45.0 (C-4), 39.0 (C-5), 37.8 (C-1''''), 35.8 (C-1''), 31.7 (C-2''''), 29.5 (C-4'); Found (ESI) 551.2935 [MNa$^+$] ($C_{38}H_{40}O_2Na$ requires 551.2921).

(3*R*,5*R*, 10*R*, 11*S*)-3,10-diphenethyl-5,11-di((*E*)-styryl)-1,5-dioxocane 159

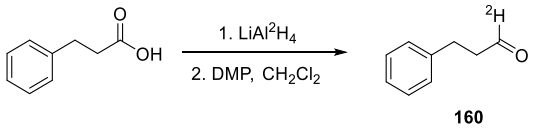


159



ν_{max} (neat)/cm^{-1} 3025, 2926, 2855, 1495; δ_H (500 MHz, $CDCl_3$) 7.42 – 7.39 (4H, m, Ar), 7.35 – 7.31 (4H, m, Ar), 7.29 – 7.24 (4H, m, Ar), 7.18 – 7.17 (3H, m, Ar), 7.13 – 7.10 (3H, m, Ar), 7.05 – 7.03 (2H, m, Ar), 6.71 (1H, d, *J* 16, 2'-H), 6.58 (1H, d, *J* 16, 2'''-H), 6.35 (1H, dd, *J* 16, 7, 1'''-H), 6.30 (1H, dd, *J* 16, 5, 1'-H), 4.52 (1H, m, 6-H), 4.16 (1H, m, 2-H), 4.00 (1H, m, 4-H), 3.84 (1H, m, 8-H), 2.90 – 2.81 (2H, m, 2''''-*H*H, 2''-*H*H), 2.71 – 2.59 (2H, m, 2''''-H*H*, 2''-H*H*), 2.15 (1H, m, 3-*H*H), 2.00 – 1.85 (2H, m, 1''-*H*H, 1''''-*H*H), 1.83 – 1.77 (3H, m, 7-*H*H, 1''''-H*H*, 3-H*H*), 1.68 (1H, m, 7-H*H*), 1.61 (1H, m, 1''-H*H*); δ_C (125 MHz, $CDCl_3$) 142.3, 142.0, 137.0, 136.8, 132.5 (C-1'''), 131.9 (C-1'), 129.4 (C-2'''), 128.6 (C-2'), 128.6, 128.6, 128.5, 128.4, 128.4, 128.3, 127.6, 127.4, 126.4, 126.4, 125.7, 125.7, 82.6 (C-2), 79.6 (C-8), 76.8 (C-4), 68.6 (C-6), 42.3 (C-7), 41.8 (C-3), 38.6 (C-1'''), 37.1 (C-1''), 32.6 (C-2''), 32.5 (C-2'''); Found (ESI) 551.2914 [MNa$^+$] ($C_{38}H_{40}O_2Na$ requires 551.2921).

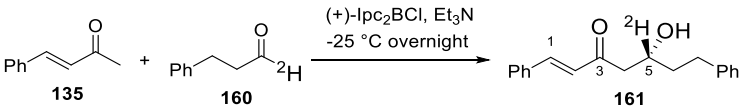
[1-^{2}H]-Dihydrocinnamaldehyde 160



160

$LiAl^2H_4$ (0.56 g, 13.32 mmol) was suspended in dry Et_2O (10 mL) and a solution of dihydrocinnamic acid (1.0 g, 6.66 mmol) in dry Et_2O (7 mL) was added at 0 °C under nitrogen. The mixture was stirred at room temperature for 1 h and diluted with Et_2O (20 mL). Water was added dropwise at 0 °C until all $LiAl^2H_4$ was quenched. The suspension was filtered through celite and the filtrate dried over $MgSO_4$ and the solvent removed *in vacuo* to give corresponding alcohol as colourless liquid (0.93 g, 99%). The alcohol was dissolved in dry CH_2Cl_2 (8 mL) under nitrogen. A solution of 15% wt of Dess-Martin periodinane in CH_2Cl_2 (2.71 mL, 1.31 mmol) was added and the mixture stirred at room temperature overnight. The solvent was removed *in vacuo* and the solid dissolved in Et_2O. The solution was filtered through celite and the solvent from filtrate removed *in vacuo*. The residue was purified by column chromatography using 2.5% EtOAc in hexane as eluent to give aldehyde **160** as a light-yellow liquid (0.1 g, 63%). δ_H (400 MHz, $CDCl_3$) 7.32 – 7.27 (2H, m, Ar), 7.23 – 7.20 (3H, m, Ar), 2.97 (2H, t, *J* 7, 3-H_2), 2.78 (2H, t, *J* 7, 2-H_2); δ_C (100 MHz, $CDCl_3$) 140.4, 128.7, 128.4, 126.4, 45.2 (C-2), 28.2 (C-3). Spectroscopic data in accord with the literature.[119]

[5-^{2}H]-(*R*,*E*)-5-hydroxy-1,7-phenylhept-1-en-3-one 161

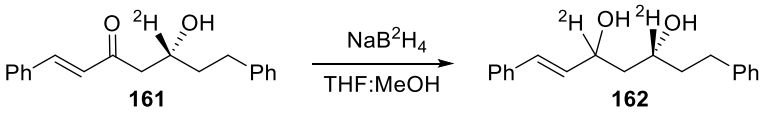


135 **160** **161**

(+)-Ipc_2BCl (4.76 mL, 4.99 mmol, 1.05 M in hexane) was dissolved in dry Et_2O (50 mL) and cooled to 0 °C. Et_3N (0.53 mL, 3.82 mmol) and a solution of 4-phenyl-3-buten-2-one **135** (0.73 g, 5.0 mmol) in dry Et_2O (10 mL) were added and the mixture stirred at 0 °C for 30 min. The mixture was cooled to −78 °C and a solution of aldehyde **160** (0.45 g, 3.33 mmol) in dry Et_2O (7 mL) was added dropwise and the mixture stirred for 30 min at −78 °C. The mixture was allowed to warm to −25 °C and stirred overnight. Saturated solution of $NaHCO_{3(aq)}$ (50 mL) was added and the aqueous layer extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 5-15% EtOAc in petroleum ether 40-60 °C as eluent to give hydroxyketone **161** as a colourless oil (0.78 g, 83%). δ_H (400 MHz, $CDCl_3$) 7.56 – 7.54 (3H, m, 1-H, Ar), 7.42 – 7.40 (3H. m, Ar), 7.31 – 7.17 (5H, m, Ar), 6.72 (1H, d, *J* 16, 2-H), 2.89 – 2.71 (4H, m, 4-H_2, 7-H_2), 1.91 (1H, m,

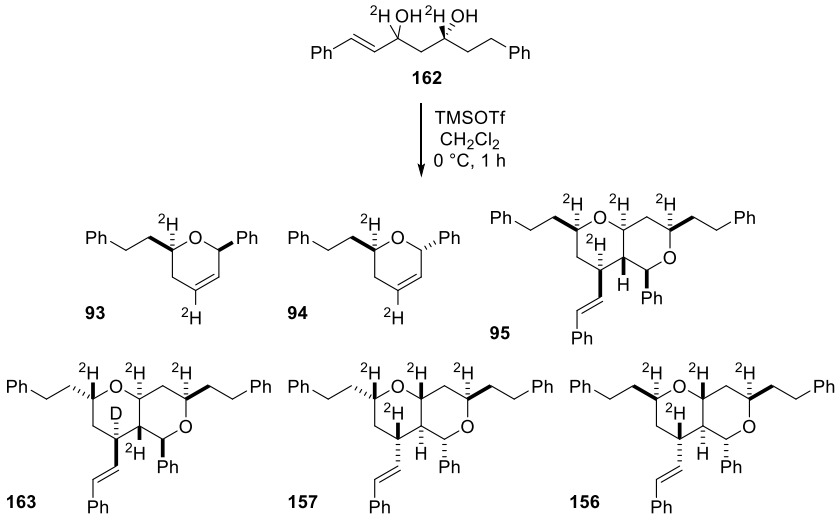
6-*H*H), 1.77 (1H, m, 6-H*H*); δ_C (100 MHz, $CDCl_3$) 200.1 (CO), 143.7 (C-1), 141.9, 134.2, 130.8, 129.0, 128.4, 126.3 (C-2), 125.9, 46.7 (C-7), 38.1 (C-6), 31.8 (C-7).

[3,5-$^2H_2$]-(5*R*, *E*)-1,7-Diphenylhept-1-ene-3,5-anti-diol 162



Hydroxyketone **161** (0.35 g, 1.24 mmol) was dissolved in a mixture 1:1 THF:MeOH and cooled to 0 °C. NaB^2H_4 (0.52 g, 12.4 mmol) was added portionwise and the mixture stirred at room temperature for 1 h. A semi-saturated solution of NH_4Cl (6 mL) was added. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers dried over $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 10-50% EtOAc in hexane as eluent to give a mixture of diastereomers **162** as a colourless oil (0.22 g, 63%). δ_H (400 MHz, $CDCl_3$) 7.39 – 7.16 (10H, m, Ar), 6.63 (1H, m, 1-H), 6.28 (1H, m, 2-H), 2.91 – 2.66 (2H, m, 7-H_2), 1.94 – 1.75 (4H, m, 6-H_2, 4-H_2); δ_C (100 MHz, $CDCl_3$) 142.0, 136.7, 132.0 (C-2), 130.3 (C-1), 128.8, 128.6, 128.5, 127.9, 126.6, 126.0, 42.8 (C-4), 39.4 (C-6), 32.3 (C-7).

Treatment of [3,5-$^2H_2$]-diol 162 with TMSOTf



[3,5-$^2H_2$]-Diol **162** (0.22 mg, 1.28 mmol) was dissolved in CH_2Cl_2 (1.5 mL) under nitrogen and the solution was cooled to 0 °C. TMSOTf (7 µL, 0.039 mmol) was added and the mixture was stirred at this temperature for 1 h. Water (1 mL) was added and the two phases separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The crude product was purified by HPLC using Waters SunFire

Prep silica column with a flow of 1 mL/min and a gradient of EtOAc with hexane isolating *syn*-dihydropyran **93** (7 mg, 3%), *anti*-dihydropyran **94** (2.3 mg, 1%), blepharocalyxin analogue **95** (8.3 mg, 4% yield), **163** (2.6 mg, 1.2% yield), **157** (3.5 mg, 1.7% yield), **156** (4.3 mg, 2% yield).

[3,5-$^2H_2$]-*Syn*-3-phenethyl-7-phenyl-3,4-dihydro-2H-pyran 93. A colourless oil. δ_H (400 MHz, $CDCl_3$) 7.41 – 7.34 (4H, m, Ar), 7.31 – 7.27 (3H, m, Ar), 7.22 – 7.17 (3H, m, Ar), 5.76 (1H, s(br), 6-H), 5.15 (1H, s(br), 7-H), 2.85 – 2.72 (2H, m, 1-H_2), 2.15 (1H, m, 4-*H*H), 2.03 – 1.95 (2H, m, 4-H*H*, 2-*H*H), 1.83 (1H, ddd, *J* 14, 9, 7, 2-H*H*).

[3,5-$^2H_2$]-*Anti*-3-phenethyl-7-phenyl-3,4-dihydro-2H-pyran 94. A colourless oil. δ_H (400 MHz, $CDCl_3$) 7.42 – 7.10 (8H, m, Ar), 6.90 – 6.89 (2H, m, Ar), 6.00 (1H, s, 6-H), 5.3 (1H, s, 7-H), 2.74 (1H, m, 1-*H*H), 2.52 (1H, m, 1-H*H*), 2.14 – 1.98 (2H, m, 4-H_2), 1.89 (1H, m, 2-*H*H), 1.69 (1H, m, 2-H*H*).

[1,3,5,9-$^2H_4$]-(1*S,3*R**,5*R**,6*R**,7*R**,9*R**)-3,9-phenylethyl-7-phenyl-5-(*E*)-phenethenyl-2,8-dioxabicyclo[4.4.0]decane 95**. A colourless oil. δ_H (500 MHz, $CDCl_3$) 7.30 – 7.07 (17H, m, Ar), 6.98 (1H, m, Ar), 6.72 (2H, m, Ar), 5.81 (1H, d, *J* 16, 2'-H), 5.13 (1H, d, *J* 16, 1'-H), 4.01 (1H, d, *J* 10, 7-H), 2.81 – 2.67 (4H, m, 2"-H2, 2"'-H_2), 2.06 (1H, d, *J* 12, 10-*H*H), 1.96 (1H, m, 1"-*H*H), 1.89 – 1.78 (2H, m, 1"-H*H*, 1"'-*H*H), 1.72-1.65 (3H, m, 6-H, 10-HH, , 1"'-H*H*), 1.53 (1H, d, *J* 13, 4-HH), 1.32 (1H, d, *J* 13, 4-HH); δ_C (120 MHz, $CDCl_3$) 142.1, 140.5, 137.4, 134.1 (C-1'), 128.5, 128.5, 128.3 (C-2'), 128.3, 128.2, 127.9, 128.9, 127.8, 126.5, 125.8, 125.7, 125.7, 83.3 (C-7), 50.5 (C-6), 40.1 (C-4), 37.9 (C-10), 37.5, 37. 3 (C-1" & C-1"'), 31.6, 31.3 (C-2" & C-2"').

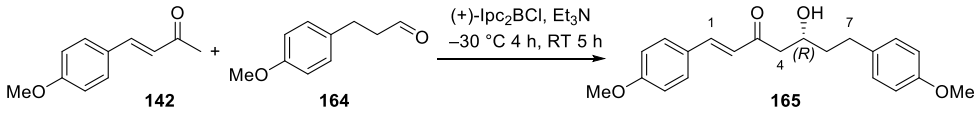
[1,3,5,9-$^2H_4$]-(1*S,3*S**,5*R**,6*R**,7*R**,9*R**)-3,9-phenylethyl-7-phenyl-5-(*E*)-phenethenyl-2,8-dioxabicyclo[4.4.0]decane 163**. A colourless oil. δ_H (500 MHz, $CDCl_3$) 7.32 – 7.07 (18H, m, Ar), 6.73 – 6.71 (2H, m, Ar), 5.77 (1H, d, *J* 16, 2'-H), 5.12 (1H, d, *J* 16, 1'-H), 4.03 (1H, d, *J* 10, 7-H), 2.78 – 2.64 (4H, m, 2''-H_2, 2'''-H_2), 2.33 (1H, m, 1''-HH), 1.95 (1H, m, 1'''-HH), 1.89 (1H, d, *J* 12, 10-*H*H) 1.82 – 1.69 (5H, m, 4-*H*H, 1''-HH, 1'''-HH, 6-H, 10-H*H*), 1.42 (1H, d, *J* 14, 4-H*H*); δ_C (125 MHz, $CDCl_3$) 142.1, 142.0, 137.4, 134.1 (C-1'), 128.6,128.5,128.5,128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 126.5 (C-2'), 125.9, 125.8, 125.7, 83.2 (C-7), 20.9 (C-6), 38.1 (C-10), 37.3 (C-1'''), 36.9 (C-4), 32.7 (C-1''), 32.9, 31.3 (C-2'' & C-2''')

[1,3,5,9-$^2H_4$]-(1*R,3*S**,5*S**,6*S**,7*S**,9*R**)-3,9-phenylethyl-7-phenyl-5-(*E*)-phenethenyl-2,8-dioxabicyclo[4.4.0]decane 157**. A colourless oil. δ_H (500 MHz, $CDCl_3$) 7.37 – 7.26 (5H, m, Ar), 7.20 – 7.14 (10H, m, Ar), 7.11 – 7.06 (3H, m, Ar), 7.00 (1H, m, Ar), 6.71 – 6.69 (2H, m, Ar), 5.83 (1H, d, *J* 16, 2'-H), 5.16 (1H, d, *J* 16, 1'-H), 4.28 (1H, d, *J* 10, 7-H), 2.80 – 2.59 (4H, m, 2''-H_2, 2'''-H_2), 2.25 (1H, m, 1'''-*H*H), 2.08 (1H, d, *J* 13, 10-*H*H), 1.96 (1H, d, J 13, 10-H*H*), 1.89 – 1.75 (4H, m,

1''-*H*H, 6-H, , 1'''-*H*H, 4-*H*H), 1.69 (1H, m, 1''-*H*H), 1.34 (1H, d, *J* 14, 4-H*H*); δ_C (100 MHz, $CDCl_3$) 142.1, 142.0, 140.9, 137.3, 134.0 (C-1'), 128.6, 128.5, 128.4, 128.3 (C-2'), 128.1, 128.0, 127.8, 126.5, 125.9, 125.8, 125.7, 76.5 (C-7), 51.4 (C-6), 39.9 (C-5), 37.6 (C-4), 35.1 (C-10), 33.3, 32.5 (C-1''' & C-1''), 31.6, 29.7 (C-2''' & C-2'').

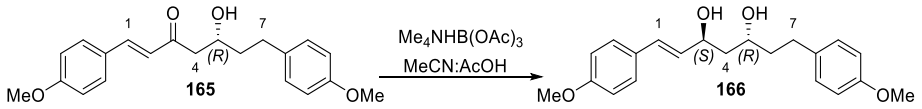
[1,3,5,9-$^2H_4$]-(1*R,3*R**,5*S**,6*S**,7*S**,9*R**)-3,9-phenylethyl-7-phenyl-5-(*E*)-phenethenyl-2,8-dioxabicyclo[4.4.0]decane 156**. A colourless oil. δ_H (500 MHz, $CDCl_3$) 7.34 – 7.15 (15H, m, Ar), 7.11 – 7.07 (3H, m, Ar), 7.02 (1H, m, Ar), 6.72-6.70 (2H, m, Ar), 5.80 (1H, d, *J* 16, 1'-H), 5.15 (1H, d, *J* 16, 2'-H), 4.29 (1H, d, *J* 10, 7-H), 2.77 – 2.57 (4H, m, 2''-H_2, 2'''-H_2), 2.34 – 2.20 (2H, m, 1''-*H*H, 1'''-*H*H), 2.15 (1H, d, *J* 14, 4-*H*H), 1.83 – 1.73 (5H, m, 10-H_2, 6-H, 1''-H*H*, 1'''-H*H*) 1.44 (1H, d, *J* 14, 4-H*H*); δ_C (125 MHz, $CDCl_3$) 142.0, 141.9, 140.8, 137.3, 133.9 (C-2'), 128.6, 128.5, 128.4, 128.2, 128.0 (C-1'), 127.9, 126.6, 125.9, 125.8, 76.3 (C-7), 50.8 (C-6), 36.6 (C-4), 35.4 (C-1''), 33.5 (C-10), 32.8 (C-1"'), 32.5, 32.4 (C-2"' & C2'').

(–)-(1*E*,5*R*)-5-Hydroxy-1,7-bis(4-methoxyphenyl)hept-1-en-3-one 165



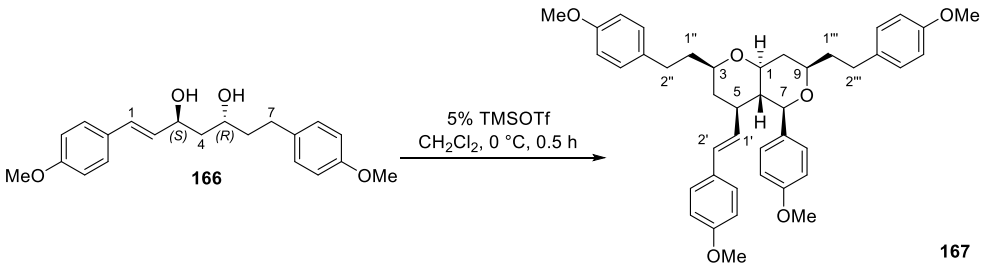
Enone **142** (0.34 g, 1.96 mmol) was dissolved in THF (25 mL) under nitrogen and the solution cooled to 0 °C. Et_3N (0.55 mL, 3.91 mmol) and (+)-Ipc_2BCl (1.42 mL, 1.2 M in hexane, 1.70 mmol) were added. After 2.5 h, the reaction mixture was cooled to −78 °C and a solution of *p*-methoxyphenylpropanal **164** (0.21 g, 1.30 mmol) was added dropwise. The temperature was increased to −30 °C and the reaction stirred overnight. The reaction mixture was allowed to warm to room temperature and stirred for 4 h, quenched with the addition of $NaHCO_3$ solution (50 mL) and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 10-40% EtOAc in hexane to give β-hydroxyketone **165** as white solid (0.20 g, 42%, *er* 9:1). mp 110-112 °C; $[\alpha]_D^{22}$−23.5 (*c*. 0.17 $CHCl_3$) δ_H (400 MHz, $CDCl_3$) 7.52 (1H, d, *J* 16, 1-H), 7.52–7.48 (2H, m, Ar-H), 7.19–7.12 (2H, m, Ar-H), 6.94–6.90 (2H, m, Ar-H), 6.85–6.81 (2H, m, Ar-H), 6.60 (1H, d, *J* 16, 2-H), 4.14 (1H, m, 5-H), 3.85 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 2.88–2.64 (4H, m, 4-H_2, 7-H_2), 1.87 (1H, m, 6-*H*H), 1.74 (1H, m, 6-H*H*); δ_C (100 MHz, $CDCl_3$) 201.0 (CO), 162.0, 157.9, 143.6 (C-1), 134.2, 130.3, 129.5, 127.0, 124.2 (C-2), 114.6, 114.0, 67.4 (C-5), 55.6 (OCH_3), 55.4 (OCH_3), 46.8 (C-7), 38.6 (C-6), 31.0 (C-4); Found (ESI) [MNa^+] 341.1742 ($C_{21}H_{24}O_4Na$ requires 341.1747).

(+)-(1*E*, 3*S*, 5*R*,)-1,7-bis(*p*-methoxy)phenylhept-1-ene-3,5-diol 166



$Me_4NHB(OAc)_3$ (1.23 g, 4.70 mmol) was dissolved in a 1:1 mixture of MeCN:AcOH (10 mL) under nitrogen and stirred for 30 min. The solution was cooled to −20 °C and a solution of hydroxyketone **165** (0.20 g, 0.59 mmol) in MeCN (5 mL) was added to the reaction mixture and stirred overnight. Semi-saturated Rochelle's salt solution (15 mL) was added and the mixture diluted with CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed repeatedly with $NaHCO_{3(aq).}$ The organic phase was dried with $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 10-40% EtOAc in hexane to give diol **166** as a white solid (0.19 g, 39% over two steps, *dr* 75:25). mp 82-84 °C; $[\alpha]_D^{22}$+2.0 (*c*. 1.0 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.31 (2H, d, *J* 9, Ar-H), 7.11 (2H, d, *J* 9, Ar), 6.87–6.80 (5H, m, Ar-H) 6.56 (1H, d, *J* 16, 1-H), 6.13 (1H, dd, *J* 16, 6, 2-H), 4.62 (1H, q, *J* 6, 3-H), 4.01 (1H, m, 5-H), 3.81 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 2.77–2.60 (2H, m, 7-H_2), 1.89–1.71 (4H, m, 4-H_2, 6-H_2); δ_C (100 MHz, $CDCl_3$) 159.5, 157.9, 134.1 (C-1), 129.8 (C-2), 129.7, 129.4, 127.8, 114.2, 114.0, 71.0 (C-3), 69.0 (C-5), 55.4 (OCH_3), 42.9 (C-4), 39.5 (C-6), 31.3 (C-7). Found (ESI) [MNa^+] 365.1714 ($C_{21}H_{26}O_4Na$ requires 365.1723).

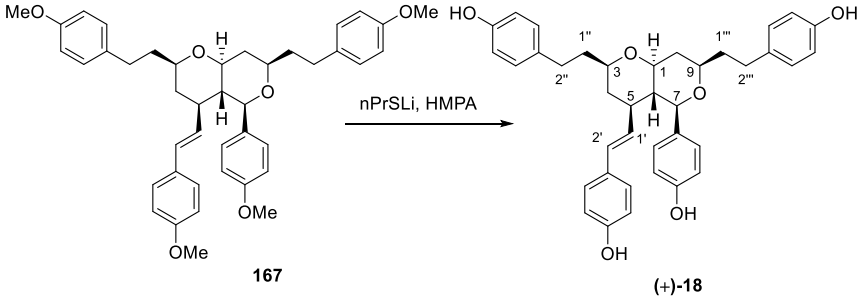
(+)-Blepharocalyxin D tetramethyl ether 167



(+)-Diol **166** (0.10 mg, 0.29 mmol) was dissolved in CH_2Cl_2 (1 mL) and the solution was cooled to 0 °C. TMSOTf (3.4 µL, 0.019 mmol) was added by microsyringe and the mixture was stirred at this temperature for 0.5 h. Water (0.5 mL) was added and the two phases separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The crude product was purified by column chromatography. Elution with 2.5% EtOAc in petroleum ether 40-60 °C gave blepharocalyxin analogue **167** (31 mg, 33% yield). $[\alpha]_D$ +93.3 (*c*.0.3, $CHCl_3$); [Lit. for the enantiomer[32] $[\alpha]_D^{22}$ −90.4 (*c*.0.32, $CHCl_3$)]; δ_H (500 MHz, Acetone-D_6) 7.11 – 7.05 (4H, m, Ar), 6.87 – 6.77 (6H, m, Ar), 6.72 – 6.66 (4H, m, Ar), 5.71 (1H, d, *J* 16, 2'-H), 4.99 (1H, d, *J* 16, 9, 1'-H), 3.95 (1H, d, *J* 10, 7-H), 3.79

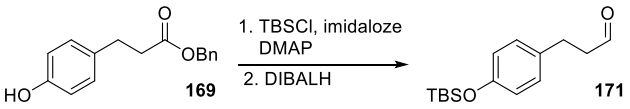
(3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.51 (1H, m, 9-H), 3.48 (3H, s, OCH_3), 3.42 (1H, m, 3-H), 3.34 (1H, m, 1-H), 2.73 – 2.60 (4H, m, 2”-H_2, 2”’-H_2), 2.11 (1H, m, 5-H), 2.04 (1H, m, 10-*H*H), 1.92 (1H, m, 1”’-*H*H), 1.87 – 1.73 (7H, m, 1”-H_2, 1”’- H*H*), 1.68 – 1.58 (6-H, 10-H*H*), 1.53 (1H, m, 4-*H*H), 1.30 (1H, m, 4-H*H*); δ_C (100 MHz, Acetone-D_6) 159.0, 158.4, 157.7, 157.6, 134.2, 134.2, 133.3, 132.2 (C-1’), 130.5, 129.4, 129.3, 126.9 (C-2’), 129.8, 113.7, 133.7, 113.3, 82.8 (C-7), 79.2 (C-1), 75.7 (C-3), 74.9 (C-9), 55.2 (OCH_3), 54.9 (OCH_3), 51.1 (C-6), 42.0 (C-5), 40.4 (C-4), 38.1 (C-10), 37.9, 37.7 (C-1” & C-1”’), 30.7, 30.4 (C-2” & C-2”’). Spectroscopic data in accord with the literature for the enantiomer[32]

(+)-Blepharocalyxin D



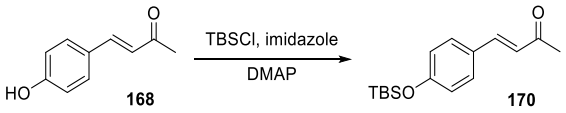
Propanethiol (0.28 mL, 3 mmol) was dissolved in HMPA (2 mL) and cooled to 0 °C under nitrogen. *n*Butyllithium (1.9 mL, 1.54 M in hexane, 3 mmol) was added dropwise and stirred for 1 h. The reaction mixture was warmed to room temperature and the hexane was removed *in vacuo*. A solution of tetramethyl ether **167** (25.4 mg, 0.037 mmol) in HMPA (1 mL) was added dropwise to the resulting solution of lithium propanethiolate. The reaction mixture was heated to 180 °C for 1 h before cooling to room temperature. Water (20 mL) was added and the mixture extracted with EtOAc (3 × 20 ml). The organic phase was dried over $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 2-10% methanol in chloroform to give (+)-blepharocalyxin D as a pale yellow solid (0.21 g, 99%). $[\alpha]_D$ +80.3 (*c*. 0.7 MeOH) [Lit. For the enantiomer[41] $[\alpha]_D^{22}$ −79.2 (*c*.0.23, MeOH)]; δ_H (500 MHz, Acetone-D_6) 7.04 – 7.00 (6H, m, Ar), 6.76 – 6.72 (6H, m, Ar), 6.68 – 6.58 (4H, m, Ar), 5.82 (1H, d, *J* 16, 2’-H), 5.07 (1H, d, *J* 16, 8, 1’-H), 3.99 (1H, d, *J* 10, 7-H), 3.52 (1H, m, 9-H), 3.46 (1H, m, 3-H), 3.37 (1H, m, 1-H), 2.69 – 2.52 (4H, m, 2”-H_2, 2”’-H_2), 2.20 (1H, m, 5-H), 2.00 (1H, m, 10-*H*H), 1.83 – 1.49 (7H, m, 1”-H_2, 1”’-H_2, 4-*H*H, 6-H, 10-H*H*), 1.29 (1H, m, 4-H*H*); δ_C (125 MHz, Acetone-D_6) 157.8, 156.9, 156.3, 133.9, 133.8, 133.7, 133.0 (C-1’), 130.6, 130.2, 130.2, 128.0 (C-2’), 127.8, 115.9, 115.6, 83.6 (C-7), 80.0 (C-1), 76.3 (C-3), 75.5 (C-9), 52.1 (C-6), 42.5 (C-5), 41.6 (C-4), 39.9 (C-10), 39.2, 39.1 (C-1” & C-1”’), 31.4, 31.3 (C-2” & C-2”’). Spectroscopic data in accord with the literature for the enantiomer.[41]

Benzyl 3-(*p*-*tert*-butyldimethylsilyloxyphenyl)propanal 171



Ester **169** (0.67 g, 2.60 mmol) was dissolved in dry CH_2Cl_2 (27 mL) under nitrogen and imidazole (0.53 g, 7.79 mmol), TBSCl (0.47 g, 3.12 mmol) and DMAP (0.032 g, 0.26 mmol) were added. After stirring at room temperature for 1.5 h, the reaction was quenched with the addition of $NH_4Cl_{(aq)}$ (10 mL). The aqueous fraction was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 2.5% EtOAc in hexane to give corresponding ester as a colourless oil (0.92 g, 95%). Ester (3.13 g, 8.44 mmol) was dissolved in dry CH_2Cl_2 (70 mL) under nitrogen and the solution was cooled to −78 °C. DIBALH (1.2 g, 8.44 mmol) was added dropwise and stirred at this temperature for 2.5 h. Methanol (20 mL) and Rochelle's salt (50 mL) were added and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and solvent removed *in vacuo.* The residue was purified by column chromatography using 2.5-5% EtOAc in petroleum ether 40-60 °C to give aldehyde **171** as a colourless oil (2.17 g, 97%). δ_H (400 MHz, $CDCl_3$) 9.81 (1H, s, 1-H), 7.03 (2H, d, *J* 6, Ar), 6.77 (2H, d, *J* 6, Ar), 2.89 (2H, t, *J* 13, 3-H_2), 2.74 (2H, t, *J* 13, 2-H_2), 0.98 (9H, s, C(C*H*$_3$)$_3$), 0.19 (6H, s, Si(C*H*$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 201.9 (C-1), 154.1, 133.0, 129.2, 120.2, 45.6 (C-2), 27.5 (C-3), 25.8 (SiC(*C*H$_3$)$_3$), 18.3 (Si*C*(CH$_3$)$_3$), −4.3 (Si(*C*H$_3$)$_2$).

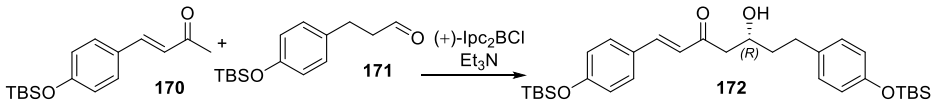
3-(*p*-*tert*-Butyldimethylsilyloxyphenyl)propional 170



Enone **168** (1.17 g, 7.21 mmol) was dissolved in anhydrous dichloromethane (50 mL) under nitrogen and imidazole (1.47 g, 31.64 mmol), TBSCl (1.30 g, 8.65 mmol) and DMAP (0.09 g, 0.72 mmol) were added. After stirring at room temperature for 1.5 h, the reaction was quenched with the addition of $NH_4Cl_{(aq)}$ (20 mL). The aqueous fraction was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 2.5% EtOAc in petroleum ether 40-60 °C to give ketone **170** as a white crystalline solid (1.81 g, 90%). δ_H (400 MHz, $CDCl_3$) 7.47 (1H, d, *J* 16, 1-H), 7.44 (2H, d, *J* 9, Ar), 6.85 (2H, d, *J* 9, Ar), 6.60 (1H, d, *J* 16, 2-H), 2.36 (3H, s, CH_3), 0.99 (9H, s, C(C*H*$_3$)$_3$), 0.22 (6H, s, Si(C*H*$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 198.5 (CO), 158.2 , 143.4

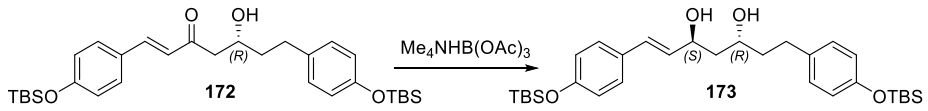
(C-1), 130.0 , 127.7 , 125.3 (C-2), 120.7 , 27.5 (CH_3) 25.7 (SiC(CH_3)$_3$), 18.3 (SiC(CH$_3$)$_3$), −4.3 (Si(CH$_3$)$_2$). Spectroscopic data in accord with the literature.[120]

(*R*,*E*)-1,7-bis(*p*-*tert*-Butyldimethylsilyloxyphenyl)-5-hydroxyhept-1-en-3-one 172



(+)-Ipc$_2$BCl (2.7 mL, 1.05 M, 2.84 mmol) was dissolved in anhydrous CH_2Cl_2 (35 mL) under nitrogen and the solution cooled to 0 °C. A solution of enone **170** (0.78 g, 2.84 mmol) in dry CH_2Cl_2 (5 mL) and Et_3N (0.79 mL, 5.67 mmol) were added and the reaction mixture was stirred at this temperature for 3 h. After cooling to −78 °C a solution of aldehyde **171** (0.5 g, 1.90 mmol) was added dropwise and the mixture stirred overnight at −30 °C. The reaction was warm up to 30 °C and stirred for 6 h. $NaHCO_{3(aq)}$ (50 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic layers dried over $MgSO_4$ and solvent removed *in vacuo*. The residue was purified by column chromatography using 1-20% EtOAc in hexane to give hydroxyketone **172** as a white solid (0.34 g, 32%). δ_H (400 MHz, $CDCl_3$) 7.50 (1H, d, *J* 16, 1-H), 7.44 (2H, d, *J* 9, Ar), 7.07 (2H, d, *J* 9, Ar), 6.85 (2H, d, *J* 9, Ar), 6.76 (2H, d, *J* 9, Ar), 6.59 (1H, d, *J* 16, 2-H), 4.13 (1H, m, 5-H), 3.39 (1H, s, OH), 7.87 – 2.62 (4H, m, 4-H_2, 7-H_2), 1.91-1.82 (1H, m, 6-*H*H), 1.77 – 1.70 (1H, m, 6H*H*), 0.99 (9H, s, C(C*H*$_3$)$_3$), 0.98 (9H, s, C(C*H*$_3$)$_3$), 0.23 (6H, s, Si(C*H*$_3$)$_2$), 0.18 (6H, s, Si(C*H*$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 201.0 (CO), 158.5 , 153.8 , 143.6 (C-1), 134.7, 130.2 , 129.4 , 127.5 , 124.4 (C-2), 120.7, 120.0, 67.4 (C-5), 46.7 (C-4), 38.5 (C-6), 31.1 (C-7), 25.8 & 25.7 (SiC(CH_3)$_3$), 18.3 (SiC(CH$_3$)$_3$), −4.3 & −4.35 (Si(CH_3)$_2$).

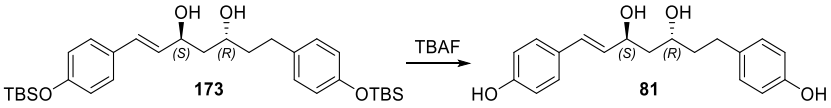
(–)-(3*S*,5*R*,*E*)-1,7-bis(*p*-*tert*-Butyldimethylsilyloxy)phenyl)hept-1-ene-3,5-diol 173



$Me_4NHB(OAc)_3$ (1.38 g, 5.23 mmol) was dissolved in a 1:1 mixture of MeCN:AcOH (2 mL) under nitrogen and stirred for 30 min. The solution was cooled to −30 °C and a solution of hydroxyketone **172** (0.35 g, 0.65 mmol) in 1:1 mixture of MeCN:THF (3 mL) was added to the reaction mixture and stirred overnight. Semi-saturated Rochelle's salt solution (3 mL) was added and aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with $NaHCO_{3(aq)}$ (2 × 5 ml). The organic phase was dried with $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by column chromatography using 5-15% EtOAc in hexane to give diol **173** as a pale-yellow oil (0.33 g, 93%, *dr* 90:10). $[\alpha]_D^{25}$ −2.0 (*c.* 1.0 acetone);

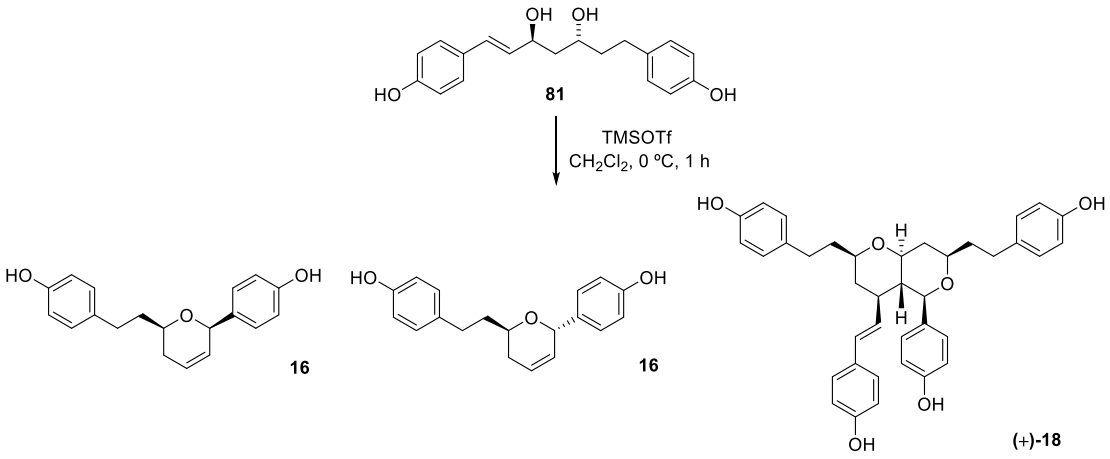
δ_H (400 MHz, acetone-d_6) 7.31 (2H, d, *J* 9, Ar), 7.10 (2H, d, *J* 9, Ar), 6.83 (2H, d, *J* 9, Ar), 6.77 (2H, d, *J* 9, Ar), 6.54 (1H, d, *J* 16, 1-H), 6.20 (1H, dd, *J* 16, 6, 2-H), 4.54 (1H, m, 3-H), 3.92 (1H, m, 5-H), 2.73 (1H, m, 7-HH), 2.61 (1H, m, 7-HH), 1.76-1.69 (4H, m, 4-H_2, 6-H_2), 0.99 (9H, s, C(C*H*$_3$)$_3$), 0.98 (9H, s, C(C*H*$_3$)$_3$), 0.21 (6H, s, Si(C*H*$_3$)$_2$), 0.19 (6H, s, Si(C*H*$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 155.0, 153.5, 135.5, 132.1 (C-2), 130.9, 127.8 (C-1), 127.4, 120.0, 119.7, 69.2 (C-3), 67.2 (C-5), 44.3 (C-4), 40.0 (C-6), 31.0 (C-7), 25.2 & 25.1 (SiC(*C*H$_3$)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), 5.2 (Si(*C*H$_3$)$_2$); Found (ESI) 565.3122 [MNa$^+$] ($C_{31}H_{50}O_4Si_2Na$ requires 565.3139).

(–)-(3*S*,5*R*,*E*)-1,7-bis(*p*-Hydroxyphenyl)hept-1-ene-3,5-diol 81



(–)-Diol **173** was dissolved in anhydrous THF (0.053 g, 0.097 mmol) under nitrogen and TBAF (1.4 mL, 1M in THF, 1.36 mmol). After stirring the reaction mixture for 1 h, water (2 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by column chromatography using 50% EtOAc in hexane to give diol **81** as a pale-yellow oil (30.5 mg, 99%). $[\alpha]_D^{25}$ −1.0 (*c*. 1.0 acetone); δ_H (500 MHz, acetone-d_6) 9.36 (1H, s, OH), 8.05 (1H, s, OH), 7.27 (2H, d, *J* 9, Ar), 7.05 (2H, d, *J* 9, Ar), 6.81 (2H, d, *J* 9, Ar), 6.75 (2H, d, *J* 9, Ar), 6.52 (1H, d, *J* 16, 1-H), 6.16 (1H, dd, *J* 16, 6, 2-H), 4.55 (1H, m, 3-H), 3.93(1H, m, 5-H), 2.71 (1H, m, 7-*H*H), 2.60 (1H, m, 7-H*H*), 1.79 – 1.66 (4H, m, 4-H_2, 6-H_2), δ_C (125 MHz, $CDCl_3$) 156.9, 155.3, 133.3, 130.9 (C-2), 129.2, 129.0, 128.1 (C-1), 127.5, 115.3, 115.0, 69.4 (C-3), 67.3 (C-5), 44.4 (C-4), 40.2 (C-6), 30.9 (C-7). Found (ESI) 319.1317 [MNa$^+$] ($C_{19}H_{20}O_3Na$ requires 319.1310).

Treatment of (–)-diol 81 with TMSOTf



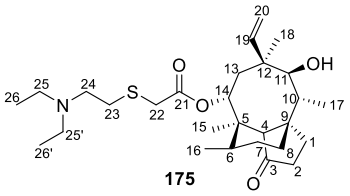
(–)-Diol **81** (30 mg, 0.095 mmol) was dissolved in a 1:1 mixture of dry CH_2Cl_2:THF (0.4 mL) under nitrogen and the solution was cooled to 0 °C. TMSOTf (0.86 µL, 0.005 mmol) was added and the mixture was stirred at this temperature for 30 min. Water (3 mL) was added and the two phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The crude product was purified by HPLC isolating *syn*-dihydropyran **16** (5 mg, 17% yield), *anti*-dihydropyran **16** (9 mg, 32% yield) and (+)-blepharocalyxin D (2 mg, 7% yield).

(3*R*,7*R*)-5,6-dehydro-4''-de-*O*- methylcentrolobine 16. A colourless oil. δ_H (500 MHz, acetone-d_6) 8.37 (1H, s, OH), 8.15 (1H, s, OH), 7.20 (2H, d, *J* 9, Ar), 7.03 (2H, d, *J* 9, Ar), 6.80 (2H, d, *J* 9, Ar), 6.74 (2H, d, *J* 9, Ar), 5.87 (1H, ddt, *J* 10, 5, 2, 5-H), 5.70 (1H, ddt, *J* 10, 3, 1, 6-H), 5.04 (1H, m, 7-H), 3.65 (1H, ddt, *J* 10, 8, 4, 3-H), 2.71 – 2.58 (2H, m, 1-H_2), 2.08 – 2.02 (2H, m, 4-H_2), 1.84 – 1.70 (2H, m, 2-H_2) δ_C (125 MHz, acetone-d_6) 156.9, 155.4, 133.1, 132.8, 130.8 (C-6), 129. , 128.4, 124.2 (C-5), 115.1, 114.9, 77.1 (C-7), 73.0 (C-3), 38.0 (C-2), 30.8 (C-4), 30.5 (C-1). Spectroscopic data in accord with the literature.[15]

(3*R*,7*S*)-5,6-dehydro-4''-de-*O*-methylcentrolobine 16. A colourless oil. δ_H (500 MHz, acetone-d_6) 8.43 (1H, s, OH), 8.05 (1H, s, OH), 7.23 (2H, d, *J* 9, Ar), 6.84 (2H, d, *J* 9, Ar), 6.71 (2H, d, *J* 9, Ar), 6.61 (2H, d, *J* 9, Ar), 5.99 (1H, m, 5-H), 5.95 (1H, ddt, *J* 10, 3, 1, 6-H), 5.14 (1H, m, 7-H), 3.46 (1H, tt, *J* 9, 5, 3-H), 2.54 (1H, ddd, *J* 14, 8, 5, 1-*H*H), 2.38 (1H, dt, *J* 14, 8, 1-H*H*) 1.98 – 1.95 (2H, m, 4-H_2), 1.71 (1H, dtd, *J* 14, 8, 5, 2-*H*H), 1.56 (1H, dtd, *J* 14 8 4, 2-H*H*); δ_C (125 MHz, acetone-d_6) 157.0, 155.2, 132.8, 132.3, 129.7, 129.3, 128.0 (C-6), 125.5 (C-5), 115.1, 114.9, 114.8, 73.5 (C-7), 65.2 (C-3), 37.9 (C-2), 31.0 (C-4), 30.3 (C-1). Spectroscopic data in accord with the literature.[18]

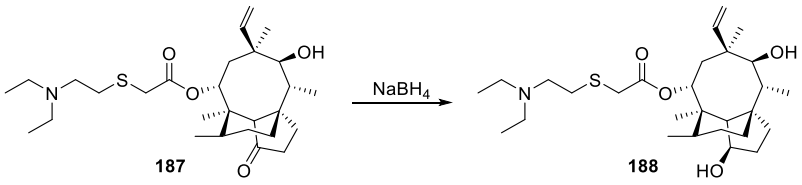
3.3 Experimental procedures chapter 2

Tiamulin 175



A solution of tiamulin (10 ml) 12.5% (Denegard®) was concentred *in vacuo* using toluene (25 ml) to azeotrope off the water to give **175** (1.25 g) as colourless oil. δ_H (400 MHz, $CDCl_3$) 6.44 (1H, dd, *J* 17, 11, 19-H), 5.70 (1H, d, *J* 8, 14-H), 5.29 (1H, dd, *J* 11, 2, 20-*H*H), 5.19 (1H, dd, *J* 17, 2, 20-H*H*), 3.36 (1H, d, *J* 6, 11-H), 3.18 (2H, dd, *J* 17, 16, 22-H_2), 3.17 – 3.06 (2H, m, 24-H_2), 3.01 (4H, q, *J* 7, 25-H_4), 2.94 – 2.86 (2H, m, 23-H_2), 2.37 – 2.01 (5H, m, 10-H, 2-H_2, 4-H, 13-H) 1.75 (1H, dd, *J* 14, 3, 8-*H*H), 1.69 – 1.59 (2H, m, 1-H_2), 1.54 (1H, m, 6-H), 1.43 (3H, s, 15-H_3), 1.39 – 1.27 (3H, m, 7-H_2, 13-H), 1.23 (6H, t, *J* 7, 26-H_6). 1.16 (3H, s, 18-H_3), 1.15 – 1.06 (1H, m, 8H*H*), 0.87 (3H, d, *J* 7, 17-H_3), 0.71 (3H, d, *J* 7, 16-H_3); δ_C (100 MHz, $CDCl_3$) 217.1 (C-3), 170.5 (C-21), 139.3 (C-19), 117.1 (C-20), 74.6 (C-11), 69.7 (C-14), 58.2 (C-4), 50.8 (C-24), 46.1 (C-25), 45.5 (C-9), 44.8 (C-13), 44.0 (C-12), 41.8 (C-5), 36.8 (C-6), 36.1 (C-10), 34.5 (C-22), 34.5 (C-2), 30.5 (C-8), 26.9 (C-7), 26.8 (C-23), 26.5 (C-18), 24.9 (C-1), 17.0 (C-16), 15.0 (C-15), 11.6 (C-17), 9.1 (C-26).Spectroscopic data in accordance with the literature data.[111]

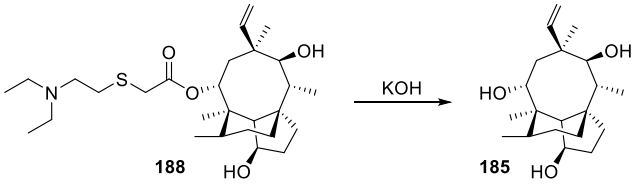
Diol 188



A solution of tiamulin **187** (3.86 g, 7.8 mmol) in EtOH:THF (1:1, 90 ml), was treated with $NaBH_4$ (4.84 g, 78.12 mmol). After stirring at room temperature for 1 day, a saturated solution of NH_4Cl (30 ml) was added. The mixture was extracted with EtOAc (2 × 50 ml) and CH_2Cl_2 (2 × 50 ml). The organic mixture was washed with brine (50 ml) and dried over $MgSO_4$, filtered and solvent evaporated *in vacuo*. The mixture reaction was purified by column chromatography using 50-80% EtOAc in petroleum ether 40-60 °C to give diol **188** as a colourless oil (1.57 g, 41%). ν_{max} (neat)/cm^{-1}: 3457, 2936, 2876, 1714; δ_H (400 MHz, $CDCl_3$) 6.50 (1H, dd, *J* 17, 11, 19-H), 5.60 (1H, d, *J* 9, 14-H,), 5.30 (1H, dd, *J* 11, 2, 20-*H*H), 5.17 (1H, dd, *J* 17, 2, 20-H*H*), 4.55 (1H, t, *J* 6, 3-H), 3.15 (3H, m, 11-H, 22-H_2), 3.01 – 2.90 (2H, m, 24-H_2), 2.92 – 2.68 (6H, m, 23-H_2, 25-H_4), 2.28 – 2.06

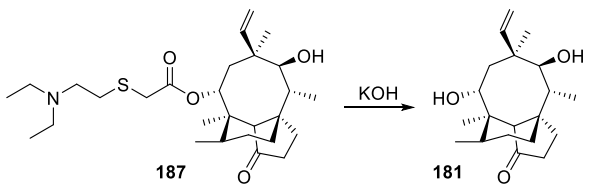
(3H, m, 6-H, 10-H, 13-*H*H), 2.04 – 1.75 (1H, m, 8-*H*H), 1.85 (1H, m, 2-*H*H), 1.73 – 1.25 (8H, m, 2-H*H*, 8-H*H*, 1-H_2, 4-H, 7-H_2, 13-H*H*), 1.22 (3H, s, 15-H_3), 1.18 (6H, td, *J* 7, 3, 26-H_6), 1.15 (3H, s, 18-H_3), 0.80 (3H, d, *J* 7, 17-H_3), 0.71 (3H, d, *J* 7, 16-H_3); δ_C (100 MHz, $CDCl_3$) 168.7 (C-21), 139.7 (C-19), 116.73 (C-20), 77.3 (C-3), 75.0 (C-11), 71.5 (C-14), 57.9 (C-24), 53.1 (C-25), 53.0 (C-23) 51.0 (C-4), 46.0 (C-9), 45.4 (C-13), 45.0 (C-12), 41.3 (C-5), 36.6 (C-6), 35.7 (C-10), 34.7 (C-22), 34.4 (C-8), 32.6 (C-2), 31.8 (C-1), 27.7 (C-7), 26.4 (C-23), 26.3 (C-18), 17.7 (C-15), 17.3 (C-16), 12.2 (C-17), 8.6 (C-26); Found (ESI) 496.3450 [MH^+] ($C_{28}H_{49}NO_4S$ requires 496.3455).

Triol 185



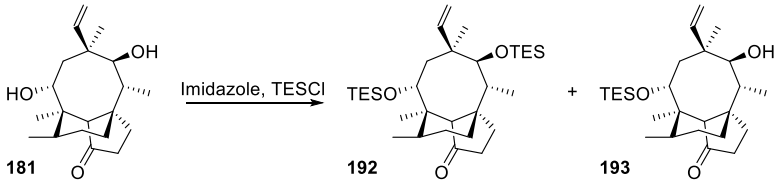
Diol **188** (0.053 g, 0.011 mmol) was added to a solution of methanol containing 5% potassium hydroxide (25 ml) and heated to reflux for 2 h. After cooling the reaction mixture was poured into water (25 ml) and the solution was extracted with CH_2Cl_2 (3 × 15 ml). The organic layers were washed with a saturated solution of $NaHCO_3$ (15 ml), dried over $MgSO_4$, filtered and solvent evaporated *in vacuo*. After purification by column chromatography using 30% EtOAc in petroleum ether 40-60 °C triol **185** was isolated as a white solid (11 mg, 32%). Mp. 180-182 °C; δ_H (400 MHz, $CDCl_3$) 6.16 (1H, dd, *J* 18, 11, 19-H), 5.31 (1H, dd, *J* 18, 1, 20-*H*H), 5.26 (1H, dd, *J* 11, 1, 20-H*H*), 4.53 (1H, t, *J* 5, 3-H), 4.32 (1H, d, *J* 8, 14-H), 3.24 (1H, t, *J* 5, 11-H), 2.29 – 2.19 (1H, m, 6-H), 2.04 (1H, br. p, *J* 7, 10-H), 2.02 – 1.91 (2H, m, 8-H*H*,13-H*H*), 1.90 – 1.79 (1H, m, 2-H*H*), 1.73 – 1.22 (8H, m, 1-H_2, 2-*H*H, 4-H, 8-*H*H, 7-H_2,13-*H*H), 1.14 (3H, s, 18-H_3), 1.13 (3H, s, 15-H_3), 0.96 (3H, d, *J* 7, 16-H_3), 0.86 (3H, d, *J* 7, 17-H_3); δ_C (100 MHz, $CDCl_3$) 140.0 (C-19), 115.6 (C-20), 77.5 (C-3), 75.5 (C-11), 68.1 (C-14), 51.9 (C-4), 46.0 (C-9), 45.7 (C-13), 45.6 (C-12), 42.1 (C-5), 36.8 (C-6), 36.1 (C-10), 34.2 (C-2), 32.4 (C-18), 32.0 (C-8), 28.5 (C-7), 27.9 (C-1), 18.6 (C-16), 16.5 (C-15), 12.0 (C-17). Spectroscopic data in accordance with the literature data.[111]

Mutilin 181



Tiamulin **187** (1.87 g, 3.79 mmol) was dissolved in methanol (100 ml) containing 5% potassium hydroxide (5 g, 89 mmol) and heated to reflux for 4.5 h. After cooling, the reaction mixture was poured into water (50 ml) and extracted with CH_2CL_2 (3 × 80 ml). The organic layers were washed with saturated $NaHCO_3$ solution (50 ml) and dried over $MgSO_4$, and solvent evaporated *in vacuo* to give diol **181** as a white solid (0.85 g, 73%). Mp. 189-191 °C [Lit. 192 °C][83]; δ_H (400 MHz, $CDCl_3$) 6.15 (1H, dd, *J* 18, 11, 19-H), 5.37 (1H, dd, *J* 18, 1, 20-*H*H), 5.29 (1H, dd, *J* 11, 1, 20H*H*), 4.35 (1H, dd, *J* 8, 6, 14-H), 3.41 (1H, dd, *J* 7, 7, 11-H), 2.29 – 2.10 (3H, m, 2-H_2, 10-H), 2.04 (1H, s, 4-H), 1.91 (1H, dd, *J* 16, 8, 13-H*H*), 1.78 – 1.37 (8H, m, 6-H, 8-H*H*, 13-H*H*, 1-H_2, 7-H_2, CHO*H*), 1.36 (3H, s, 15-H_3), 1.25 (1H, d, *J* 6, CHO*H*), 1.16 – 1.08 (1H, m, 8-*H*H), 1.15 (3H, s, 18-H_3), 0.96 (3H, d, *J* 7, 16-H_3), 0.92 (3H, d, *J* 7, 17-H_3); δ_C (100 MHz, $CDCl_3$) 217.6 (C-3), 139.4 (C-19), 115.9 (C-20), 75.2 (C-11), 66.8 (C-14), 59.1 (C-4), 45.4 (C-9), 45.3 (C-12), 45.1 (C-13), 42.4 (C-5), 36.9 (C-6), 36.6 (C-10), 34.5 (C-2), 30.5 (C-8), 28.6 (C-18), 27.2 (C-7), 25.2 (C-1), 18.3 (C-16), 13.5 (C-15), 11.3(C-17). Spectroscopic data in accordance with the literature data.[84]

Mono- and di-protected mutilins 192 and 193



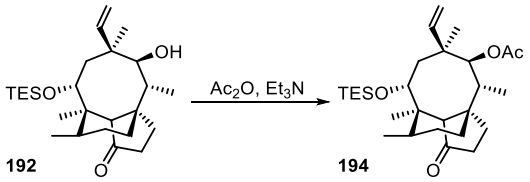
To a solution diol **181** (5.44 g, 16.99 mmol) in DMF (20 ml) were added imidazole (3.47 g, 50.96 mmol), DMAP (catalytic amount) at room temperature, then TESCl (4.28 ml, 25.48 mmol) was added at 0 °C under N_2. After stirring at room temperature for 20 h, water (120 ml) was added. The mixture was extracted with EtOAc (4 × 50 ml). The combined organic layers were washed with a saturated solution of brine (50 ml), dried over $MgSO_4$, filtered and solvent concentred *in vacuo*. The residue was purified by silica gel column chromatography using 30% EtOAc in petroleum ether 40-60 °C to give di-protected mutilin **192** (3.20 g, 34%) and mono-protected mutilin **193** (3.47 g, 47%) as colourless oils.

Di-protected mutilin **193**; IR ν_{max} (neat)/cm^{-1}: 2953, 2912, 2876, 1735; δ_H (400 MHz, $CDCl_3$) 6.15 (1H, dd, *J* 18, 11, 19-H), 5.26 (1H, dd, *J* 18, 2, 20-*H*H), 5.21 (1H, dd, *J* 11, 2, 20-H*H*), 4.47 (1H, d, *J* 8, 14-H), 3.54 (1H, d, *J* 6, 11-H), 2.30 (1H, p, *J* 7, 10-H), 2.24 – 2.16 (2H, m, 2-H_2), 2.02 (1H, s, 4-H), 1.86 (1H, dd, *J* 6, 8, 13-H*H*), 1.75 (1H, dq, *J* 14, 3, 8-H*H*), 1.60 – 1.29 (7H, m, 6-H, 1-H_2, 7-H_2, 8-*H*H, 13-*H*H), 1.34 (3H, s, 15-H_3), 1.10 (3H, s, 18-H_3), 1.03 – 0.87 (18H, m, $SiCH_2CH_3$), 0.87 (3H, d, *J* 7, 16-H_3), 0.85 (3H, d, *J* 7, 17-H_3), 0.71 – 0.56 (6H, m, $SiCH_2$), 0.58 – 0.45 (6H, m, $SiCH_2$); δ_C

(100 MHz, $CDCl_3$) 218.2 (C-3), 141.1 (C-19), 116.0 (C-20), 77.3 (C-11), 67.5 (C-14), 59.4 (C-4), 47.3 (C-13), 45.7 (C-9), 45.1 (C-12), 43.7 (C-5), 37.6 (C-6), 36.4 (C-10), 34.8 (C-2), 31.0 (C-8), 28.9 (C-18), 27.3 (C-7), 25.6 (C-1), 18.4 (C-16), 14.4 (C-15), 12.0 (C-17), 7.6 ($SiCH_2\mathit{C}H_3$), 7.3 ($SiCH_2\mathit{C}H_3$), 6.2 ($Si\mathit{C}H_2$), 5.8 ($Si\mathit{C}H_2$); Found (ESI) 571.3933 [MNa^+] ($C_{32}H_{60}O_3Si_2Na$ requires 571.3979).

Mono-protected mutilin **192**: ν_{max} (neat)/cm^{-1}: 3477, 2954, 2933, 2876, 1731; δ_H (400 MHz, $CDCl_3$) 6.25 (1H, dd, *J* 17, 11, 19-H), 5.39 (1H, dd, *J* 11, 1, 20-*H*H), 5.31 (1H, dd, *J* 17, 1, 20-H*H*), 4.54 (1H. d, *J* 8, 14-H), 3.34 (1H, t, *J* 8, 11-H), 2.28 (1H, p, *J* 7, 10-H), 2.23 – 2.11 (2H, m, 2-H_2), 2.07 – 1.98 (1H, m, 4-H), 1.97 (1H, dd, *J* 16, 8, 13-H*H*), 1.75 (1H, dd, *J* 14, 3, 8-H*H*), 1.67 – 1.36 (6H, m, 6-H,1-H_2,13-*H*H,7-H_2), 1.34 (3H, s, 15-H_3), 1.26 – 1.09 (1H, m, 8-*H*H), 1.17 (3H, s, 18-H_3), 0.94 (9H, t, *J* 8 $SiCH_2C\mathit{H_3}$), 0.89 (3H, d, *J* 4, 16-H_3), 0.86 (3H, d, *J* 6, 17-H_3), 0.61 (6H, q, *J* 8, $SiC\mathit{H_2}$); δ_C (100 MHz, $CDCl_3$) 218.0 (C-3), 139.4 (C-19), 117.9 (C-20), 75.0 (C-11), 66.6 (C-14), 59.2 (C-4), 46.8 (C-13), 45.5 (C-9), 44.3 (C-12), 43.7 (C-5), 37.6 (C-6), 35.9 (C-10), 34.7 (C-2), 30.9 (C-8), 27.3 (C-7), 26.5 (C-18), 25.0 (C-1), 18.4 (C-16), 14.3 (C-15), 11.6 (C-17), 7.2 ($SiCH_2\mathit{C}H_3$), 6.1 ($Si\mathit{C}H_2$); Found (ESI) 457.3032 [MNa^+] ($C_{26}H_{46}O_3SiNa$ requires 457.3114).

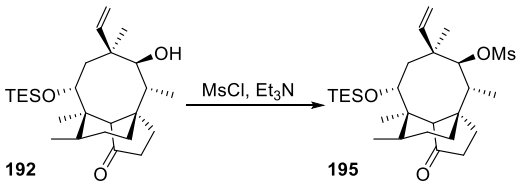
11-Acetoxy-14-methylsilyl mutilin 194



To a solution of mono-protected mutilin **192** (0.10 g, 0.243 mmol) in CH_2Cl_2 (5 ml), were added Ac_2O (2.5 ml) and Et_3N (2.5 ml). After stirring the reaction mixture at room temperature during 3 h, 1M HCl solution (15 ml) was added and the mixture was extracted with CH_2Cl_2 (4 × 10 ml), the organic layers were dried over $MgSO_4$ and solvent concentred *in vacuo* to give acetate **194** as a colourless oil (0.06 g, 56%). ν_{max} (neat)/cm^{-1}: 2984, 2954, 2936, 2876, 1730; δ_H (400 MHz, $CDCl_3$) 6.20 (1H, dd, *J* 18, 11, 19-H), 5.28 (1H, dd, *J* 18, 1, 20-*H*H), 5.28 (1H, dd, *J* 11, 1, 20-H*H*), 4.85 (1H, d, *J* 7, 11-H), 4.44 (1H. d, *J* 8, 14-H), 2.44 (1H, p, *J* 7, 10-H), 2.35 – 2.23 (1H, m, 2-H_2), 2.11 (1H, s, 4-H), 2.05 (3H, s, $COC\mathit{H_3}$), 2.00 (1H, dd, *J* 16, 8, 13-H*H*), 1.93 – 1.82 (1H, m, 1-H*H*), 1.70 (1H, m, 8-H*H*), 1.64 – 1.21 (5H, m, 6-H, 7-H_2, 13-*H*H, 1-*H*H), 1.35 (3H, s, 15-H_3), 1.21 – 1.05 (1H, m, 8-*H*H), 1.00 (3H, s, 18-H_3), 0.94 (9H, t, *J* 8, $SiCH_2C\mathit{H_3}$), 0.87 (3H, d, *J* 7, 16-H_3), 0.77 (3H, d, *J* 7, 17-H_3), 0.62 (6H, q, *J* 8, $SiC\mathit{H_2}$). δ_C (100 MHz, $CDCl_3$) 218.1 (C-3), 170.6 (CO), 140.2 (C-19), 116.3 (C-20), 77.0 (C-11), 67.1 (C-14), 59.4 (C-4), 47.2 (C-13), 45.4 (C-12), 43.7 (C-9), 43.1 (C-5), 37.6 (C-6), 35.6 (C-10), 34.7 (C-2), 30.8 (C-8), 27.4 (C-7), 27.1 (C-18), 25.1 (C-1), 20.8 ($COC\mathit{H_3}$),

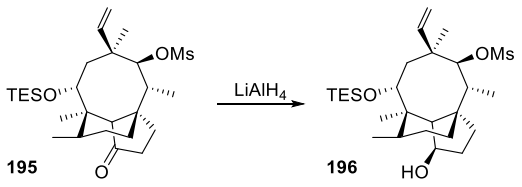
18.4 (C-16), 14.4 (C-15), 11.8 (C-17), 7.2 ($SiCH_2CH_3$), 6.2 ($SiCH_2$); Found (ESI) 499.3206 [MNa^+] ($C_{28}H_{48}O_4SiNa$ requires 499.3220).

Mesylate 195



To a solution of silyl ester **192** (0.52 g, 1.20 mmol) in CH_2Cl_2, were added Et_3N (0.50 ml, 3.61 mmol) and DMAP (catalytic amount). Then MsCl (0.14 ml, 1.80 mmol) was added dropwise slowly at 0 °C under N_2. After stirring at room temperature for 18 h, were added water (10 ml) and 1N HCl solution (1 ml). The mixture was extracted with CH_2Cl_2 (4 × 5 ml). The combined organic layers were washed with a semi-saturated solution of $NaHCO_3$ (20 ml) and brine (20 ml), dried over $MgSO_4$, filtered and solvent evaporated. The residue was purified by silica gel column chromatography using 60% EtOAc in petroleum ether 40-60 °C to give mesylate **195** as a colourless oil (0.19 mg, 30%). ν_{max} (neat)/cm^{-1}: 2961, 2929, 2875, 1731; δ_H (400 MHz, $CDCl_3$) 6.18 (1H, dd, *J* 17, 11, 19-H), 5.32 (1H, dd, *J* 2,1, 20-*H*H), 5.28 (1H, dd, *J* 8, 1, 20-H*H*), 4.65 (1H, d, *J* 7, 11-H), 4.44 (1H, d, *J* 8, 14-H), 3.02 (3H, s, C*H*$_3$SO), 2.50 (1H, p, *J* 7, 10-H), 2.32 – 2.11 (1H, m, 2-H_2), 2.08 – 1.97 (1H, m, 13-H*H*), 1.98 (1H, s, 4-H), 1.93 – 1.81 (1H, m, 1-H*H*), 1.74 (1H, dd, *J* 14, 3, 8-H*H*), 1.58 (1H, m, 6-H), 1.50 – 1.35 (4H, m, 13-*H*H,7-H_2,1-*H*H), 1.34 (3H, s, 15-H_3), 1.22 (3H, s, 18-H_3), 1.23 – 1.06 (1H, m, 8-*H*H), 1.01 (3H, d, *J* 7, 17-H_3), 0.94 (9H, t, *J* 8, $SiCH_2CH_3$), 0.86 (4H, d, *J* 7, 16-H), 0.61 (6H, q, *J* 8, $SiCH_2$). δ_C (100 MHz, $CDCl_3$) 217.2 (C-3), 138.8 (C-19), 117.4 (C-20), 87.1 (C-11), 66.9 (C-14), 59.3 (C-4), 47.0 (C-13), 45.6 (C-9), 43.9 (C-5), 43.7 (C-12), 38.7 (CH_3SO), 37.4 (C-6), 35.7 (C-10), 34.7 (C-2), 30.8 (C-8), 28.2 (C-18), 27.2 (C-7), 24.8 (C-1), 18.3 (C-16), 14.3 (C-15), 12.6 (C-17), 7.2($SiCH_2CH_3$), 6.1($SiCH_2$).); Found (ESI) 529.3260 [MOH] ($C_{27}H_{48}O_5SSiOH$ requires 529.3019).

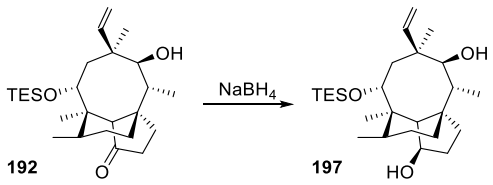
Alcohol 196



To a solution of $LiAlH_4$ (9.30 mg, (0.24 mmol) in THF (0.25 ml) was added dropwise a solution of **195** in THF (0.150 ml) at 0 °C under N_2. After stirring at room temperature for 23 h, the reaction

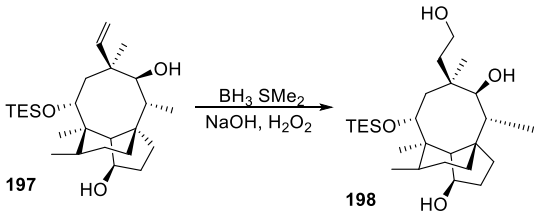
mixture was cooled, water (2 ml) and solution of 1N HCl (2 ml) were added. The mixture was extracted with EtOAc (4 × 4 ml). The combined organic layers were dried over $MgSO_4$, filtered and solvent evaporated *in vacuo* to give alcohol **196** as a colourless oil (30 mg, 71%). ν_{max} (neat)/cm^{-1}: 3473, 2954, 2934, 2875; δ_H (400 MHz, $CDCl_3$) 6.21 (1H, dd, *J* 17, 11, 19-H), 5.29 (1H, dd, *J* 3, 1, 20-*H*H), 5.26 (1H, dd, *J* 8, 1, 20-H*H*), 4.54 (2H, m, 3-H, 11-H), 4.41 (1H, d, *J* 9, 14-H), 3.01 (3H, s, *C*H_3SO), 2.35 (1H, p, *J* 7, 10-H), 2.22 – 2.10 (1H, m, 6-H), 2.10 – 1.94 (2H, m, 2-H*H*, 13-H*H*), 1.93 – 1.77 (2H, m, 8-H*H*, 1-H*H*), 1.76 – 1.51 (2H, m, 8-*H*H, 2-*H*H), 1.50 – 1.24 (5H, m, 1-*H*H, 13-*H*H, 7-H_2, 4-H), 1.22 (3H, s, 18-H_3), 1.11 (3H, s, 15-H_3), 0.95 (12H, m, 17-H_3, $SiCH_2CH_3$), 0.87 (3H, d, *J* 7, 16-H_3), 0.62 (6H, q, *J* 8, $SiCH_2$); δ_C (100 MHz, $CDCl_3$) 139.3 (C-19), 116.8 (C-20), 88.3 (C-11), 77.7 (C-3), 68.3 (C-14) 52.0 (C-4), 47.7 (C-9), 45.9 (C-13), 44.6 (C-5), 43.1 (C-12), 38.8 (*C*H_3SO), 37.2 (C-6), 35.4 (C-10), 34.2 (C-2), 33.3 (C-8), 31.8 (C-1), 28.1 (C-18), 28.0 (C-7), 18.7 (C-16), 17.4 (C-15), 13.3 (C-17), 7.2 ($SiCH_2CH_3$), 6.2 ($SiCH_2$). Found (ESI) 537.3022 [MNa^+] ($C_{27}H_{50}O_5SSiNa$ requires 537.3046).

Diol 197



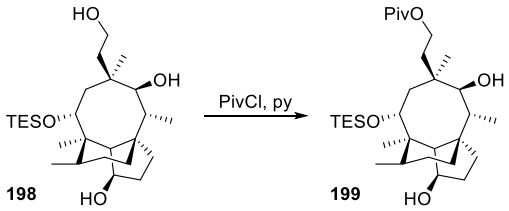
A solution of alcohol **192** (0.90 g, 2.08 mmol) in EtOH:THF (1:1, 10 ml) was treated with $NaBH_4$ (0.79 g, 20.78 mmol). After stirring at room temperature for 23 h, saturated solution of NH_4Cl (10 ml) was added carefully at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 10 ml). The combined organic extracts were washed with brine (20 ml) and dried over $MgSO_4$, filtered and solvent evaporated *in vacuo* to give diol **197** as a colourless oil (0.88 g, 92%). ν_{max} (neat)/cm^{-1}: 3465, 2953, 2875, 1728; δ_H (400 MHz, $CDCl_3$) 6.26 (1H, dd, *J* 17, 11, 19-H), 5.35 (1H, dd, *J* 11, 2, 20-*H*H), 5.27 (1H, dd, *J* 17, 1, 20-H*H*), 4.50 (2H, m, 3-H, 14-H), 3.17 (1H, dd, *J* 10, 6, 11-H), 2.19 – 2.09 (2H, m, 10-H, 6-H), 2.02 (1H, dd, *J* 16, 9, 13-H*H*), 1.98 – 1.77 (2H, m, 2-H*H*, 8-H*H*), 1.72 (1H, dd, *J* 14, 3, 8-*H*H), 1.67 – 1.56 (3H, m, 2-H, 7-H_2), 1.49 – 1.34 (4H, m, 4-H, 13-*H*H, 1-H_2), 1.26 (1H, d, *J* 10, CHO*H*), 1.17 (3H, s, 18-H_3), 1.11 (3H, s, 15-H_3), 0.95 (9H, t, *J* 8, $SiCH_2CH_3$), 0.89 (3H, d, *J* 7, 16-H_3), 0.82 (3H, d, *J* 7, 17-H_3), 0.61 (3H, q, *J* 8, $SiCH_2$); δ_C (100 MHz, $CDCl_3$) 140.0 (C-19), 117.3 (C-20), 77.9 (C-3), 75.5 (C-11), 68.1 (C-14), 51.6 (C-4), 47.5 (C-13), 45.9 (C-12), 45.2 (C-9), 43.1 (C-5), 37.5 (C-6), 35.5 (C-10), 34.2 (C-2), 33.4 (C-8), 32.0 (C-7), 28.2 (C-1), 26.6 (C-18), 18.8 (C-16), 17.4 (C-15), 12.3 (C-17), 7.3 ($SiCH_2CH_3$), 6.2 ($SiCH_2$); Found (ESI) 459.3108 [MNa^+] ($C_{26}H_{48}O_3SiNa$ requires 459.3270).

Triol 198



To a solution of diol **197** in THF (25 ml) was added $BH_3{\cdot}SMe_2$ (13.75 ml, 27.50 mmol) dropwise at −78 °C under N_2. After stirring at room temperature for 6 h, the reaction mixture was cooled at 0 °C and 2M NaOH (25 ml) and H_2O_2 (25 ml) were added. The resulting mixture was stirred at room temperature for 15 h, and then K_2CO_3 was added until saturation. The mixture was extracted with EtOAc (4 × 40 ml). The combined organic layer was washed with brine (45 ml), dried over $MgSO_4$ and solvent concentred *in vacuo*. The residue was purified by silica gel column chromatography using 30% EtOAc in petroleum ether 40-60 °C to give triol **198** as a white solid (1.18 g, 76%). Mp. 180-182 °C; ν_{max} (neat)/cm^{-1}: 3172, 2951, 2927, 2907, 2874; δ_H (400 MHz, $CDCl_3$) 4.52 (1H, t, *J* 6, 3-H), 4.37 (1H, d, *J* 9, 14-H), 3.82 (1H, td, *J* 11, 3, 20-*H*H), 3.76 – 3.66 (1H, m, 20-H*H*), 3.18 (1H, d, *J* 6, 11-H), 2.29 (1H, td, *J* 10, 5, 19-*H*H), 2.20 – 2.02 (2H, m, 6-H, 10-H), 2.01 – 1.88 (3H, m, 13-H*H*, 7-H*H*, 1-H*H*), 1.83 (1H, td, *J* 13, 5, 1-*H*H), 1.72 (1H, dd, *J* 14, 3, 8-H*H*), 1.67 – 1.19 (8H, m, 2-H_2, 7-*H*H, 4-H, 19-H*H*, 1-*H*H, 13-*H*H), 1.10 (3H, s, 18-H_3), 1.09 (3H, s, 15-H_3), 0.97 (9H, t, *J* 8, $SiCH_2C\mathit{H_3}$), 0.90 (3H d, *J* 7, 17-H_3), 0.87 (3H, d, *J* 7, 16-H_3), 0.64 (6H, m, $SiC\mathit{H_2}$); δ_C (100 MHz, $CDCl_3$) 77.9 (C-3), 75.4 (C-11), 68.3 (C-14), 58.8 (C-20), 51.6 (C-4), 50.7 (C-13), 46.0 (C-9), 43.2 (C-12), 41.7 (C-5), 38.1 (C-19), 37.3 (C-6), 34.9 (C-10), 34.0 (C-2), 32.7 (C-8), 32.1 (C-7), 28.2 (C-1), 26.7 (C-18), 18.8 (C-16), 17.5 (C-15), 11.8 (C-17), 7.3 ($SiCH_2\mathit{C}H_3$), 6.4 ($Si\mathit{C}H_2$); Found (ESI) 455.1901 [M^+] ($C_{26}H_{51}O_4Si$ requires 455.3551).

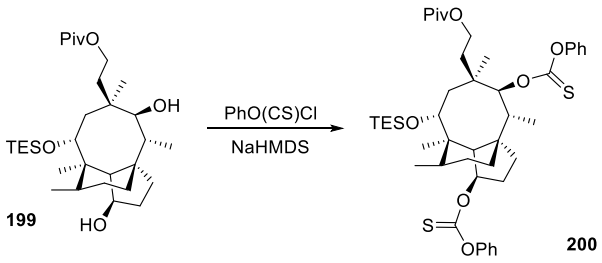
Pivaloate ester 199



To a solution of triol **198** in pyridine (20 ml) pivaloyl chloride (0.34 ml) was added dropwise at 0 °C. After stirring at room temperature for 1.5 h, MeOH (10 drops) was added and the reaction mixture was diluted with EtOAc (50 ml). The resulting solution was washed with 0.5M HCl (10 × 30 ml) and saturated solution of $NaHCO_3$ (30 ml), dried over $MgSO_4$ and solvent evaporated *in vacuo*. The residue was purified by column chromatography using 15-25% EtOAc in petroleum

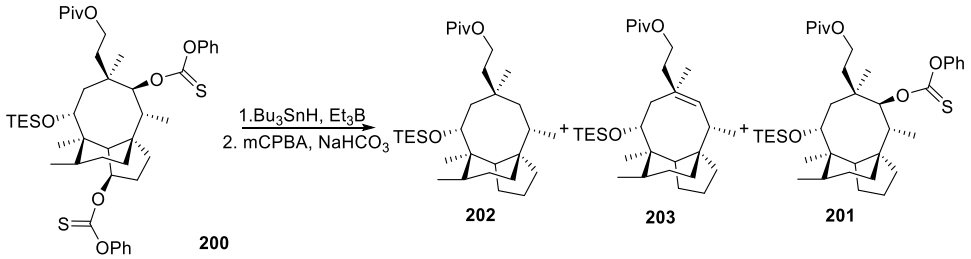
ether 40-60 °C to give pivaloate ester **199** as a colourless oil (0.70 mg, 71%). ν_{max} (neat)/cm^{-1}: 3522, 2954, 2936, 2875, 1709; δ_H (400 MHz, $CDCl_3$) 4.51 (1H, t, *J* 6, 3-H), 4.37 (1H, d, *J* 9, 14-H), 4.32 (1H, dd, *J* 11, 6, 19-*H*H), 4.20 (1H, td, *J* 11, 5, 19-H*H*), 3.21 (1H, d, *J* 6, 11-H), 2.23 (1H, ddd, *J* 14, 11, 6, 20-*H*H), 2.18 – 2.02 (2H, m, 6-H, 10-H), 1.97 – 1.78 (2H, m, 2-H*H*, 8-H*H*), 1.71 (1H, d, *J* 13, 8-*H*H), 1.68 – 1.58 (1H, m, 2-*H*H), 1.55 – 1.33 (7H, m, 1-H_2, 7-H_2, 4-H, 13-*H*H, 20-H*H*), 1.21 (9H, s, OCH_3), 1.09 (6H, s, 15-H_3, 18-H_3), 0.95 (12H, q, *J* 8, 17-H_3, $SiCH_2CH_3$), 0.87 (3H, d, *J* 7, 16-H_3), 0.63 (6H, qd, *J* 8, 2, $SiCH_2$); δ_C (100 MHz, $CDCl_3$) 178.6 (CO), 77.8 (C-3), 76.2 (C-11), 68.5 (C-14), 62.7 (C-20), 51.6 (C-4), 48.4 (C-13), 46.0 (C-9), 43.2 (C-12), 41.2 (C-5), 38.7 ($COCCH_3$), 37.3 (C-6), 34.7 (C-10), 34.1 (C-2), 33.1 (C-19), 32.8 (C-8), 32.1 (C-7), 28.2 (C-1), 27.3 (3-$COCCH_3$), 27.2 (C-18), 18.9 (C-16), 17.5 (C-15), 11.9 (C-17), 7.3 ($SiCH_2CH_3$), 6.3 ($SiCH_2$); Found (ESI) 561.3948 [MNa^+] ($C_{31}H_{58}O_5SiNa$ requires 561.3946).

Diphenoxythiocarbonyl ester 200



To a solution of **199** (0.31 g, 0.58 mmol) and PhO(CS)Cl (0.32 ml, 2.30 mmol) in THF (4 ml) was added dropwise NaHMDS (2.88 ml, 2.88 mmol) at −78 °C under N_2. After stirring for 30 min the reaction mixture was diluted with EtOAc (35 ml) and washed with semi-saturated solution of brine (30 ml), dried over $MgSO_4$ and solvent evaporated *in vacuo*. The residue was purified by column chromatography using 15-25% diethyl ether in petroleum ether 40-60 °C to give diphenoxythiocarbonyl ester **200** as pale-yellow oil (0.42 g, 96%): ν_{max} (neat)/cm^{-1}: 2957, 2936, 2875, 1725, 1489; δ_H (400 MHz, $CDCl_3$) 7.41 (4H, dd, *J* 8, 7, Ar), 7.29 (2H, dd, *J* 7, 1, Ar), 7.08 (4H, dd, *J* 11, 8 Ar), 5.85 (1H, t, *J* 5, 3-H), 5.29 (1H, d, *J* 6, 11-H), 4.36 (1H, d, *J* 9, 14-H), 4.29 (1H, td, *J* 11, 6, 19-*H*H), 4.17 (1H, td, *J* 11, 5, 19-H*H*), 2.42 – 2.27 (2H, m, 10-H, 20-*H*H), 2.23 – 1.98 (3H, m, 2-H*H*, 7-H*H*, 13-H*H*), 1.93 – 1.83 (2H, m, 4-H, 7-*H*H), 1.76 (1H, ddd, *J* 12, 7, 4, 8-H*H*), 1.68 – 1.24 (3H, m, 8-*H*H, 20-H*H*, 2-*H*H), 1.22 (9H, s, 3-$COCH_3$), 1.10 (3H, s, 18-H_3), 1.02 – 0.93 (13H, m, 15-H_3, $SiCH_2CH_3$, 17-H_3), 0.88 (3H, d, *J* 2, 16-H_3), 0.64 (6H, qd, *J* 8, 2, $SiCH_2$); δ_C (100 MHz, $CDCl_3$) 194.8 (CS), 178.5 (CO), 153.3 , 129.6, 126.5, 122.0, 92.0 (C-3), 89.9 (C-11), 67.9 (C-14), 61.9 (C-20), 51.8 (C-4), 47.9 (C-13), 46.0 (C-9), 42.8 (C-12), 41.47 (C-5), 36.5 (C-22), 36.0 (C-6), 33.8 (C-10), 33.1 (C-19), 32.4 (C-2), 30.0 (C-8), 28.1 (C-7), 27.3 (C-1), 26.3 ($COCCH_3$), 18.8 (C-16), 17.6 (C-15), 12.9 (C-17), 7.3 ($SiCH_2CH_3$), 6.4 ($SiCH_2$); Found (ESI) 833.3908 [MNa^+] ($C_{45}H_{66}O_7S_2SiNa$ requires 833.3911).

Pivaloyl ester 202 and phenoxythiocarbonyl ester 201



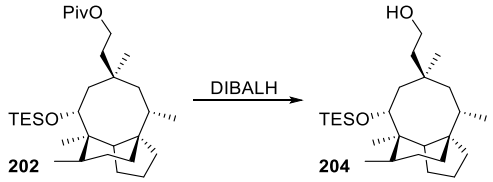
To a solution of ester **200** (0.41 g, 0.55 mmol) and Bu_3SnH (0.60 ml, 2.22 mmol) in benzene (6 ml) was added Et_3B (1.1 ml, 1.1 mmol) at 0 °C under N_2. After stirring at 0 °C during 3 h was added water (10 ml). The resulting mixture was extracted with Et_2O (4 × 10 ml). The combined organic layers were washed with saturated solution of brine (5 ml), dried over $MgSO_4$ and solvent evaporated *in vacuo*. The residue was purified by column chromatography using 1-15% diethyl ether in hexane to give a 3:2 mixture of deoxygenated compounds **202** and **203** (0.11 g, 53%) and 3-deoxy product **201** (20 mg, 8%) which was converted in **202** (10 mg, 63%) under the same deoxygenation conditions. To a solution of $NaHCO_3$ (0.15 g, 1.78 mmol) and *m*CPBA (51 mg, 0.30 mmol) in CH_2Cl_2 (1.5 ml) was added dropwise a solution of the mixture of **202** and **203** (0.15 g, 0.30 mmol) in CH_2Cl_2 (1.5 ml) at 0 °C. After stirring at this temperature for 2 h, was added saturated solution of Na_2SO_3 (9 ml). The resulting mixture was stirred for 15 min and extracted with Et_2O (3 × 10 ml). The organics layers were washed with saturated solution of $NaHCO_3$ (20 ml) and brine (10 ml), dried over anhydrous $MgSO_4$ and solvent evaporated *in vacuo*. The residue was purified by silica gel column chromatography using 1% diethyl ether in hexane to give deoxygenated product **202** as a colourless oil (71 mg, 80%).

Di-deoxygenated **202**: ν_{max} (neat)/cm^{-1}: 2957, 2933, 2873, 1730, 1458; δ_H (400 MHz, $CDCl_3$) 4.39 (1H, d, *J* 8, 14-H), 4.26 – 4.08 (2H, m, 20-H_2), 2.32 – 2.18 (1H, m, 19-*H*H), 1.97 (1H, dd, *J* 15, 8, 13-H*H*), 1.91 – 1.24 (17H, m), 1.21 (9H, s, COC*H*$_3$), 1.01 – 0.92 (9H, m, $SiCH_2CH_3$), 0.94 (3H, s, 18-H_3), 0.88 (3H, d, *J* 7, 16-H_3), 0.85 – 0.82 (9H, m, 15-H_3,17-H_3), 0.69 – 0.52 (3H, m, SiCH_2); δ_C (100 MHz, $CDCl_3$) 178.6 (CO), 68.5 (C-14), 61.8 (C-20), 49.8 (C-13), 47.4 (C-4), 46.0 (C-9), 42.4 (C-12), 40.7 (C-11), 38.8 (C-5), 36.6 (C-19), 35.2 (CO*C*CH_3), 35.2 (C-6), 33.8 (C-8), 31.1 (C-18), 30.4 (C-10), 29.8 (C-7), 29.0 (C-1), 28.2 (C-3), 27.3 (3-COC*C*H_3), 20.9 (C-15), 19.2 (C-2), 18.8 (C-16), 18.0 (C-17), 7.3 ($SiCH_2CH_3$), 6.4 (SiCH_2); Found (ESI) 529.4064 [MNa^+] ($C_{31}H_{58}O_3SiNa$ requires 529.4053).

Mono-deoxygenated **201**: ν_{max} (neat)/cm^{-1}: 2957, 2934, 2875, 1727; δ_H (400 MHz, $CDCl_3$) 7.44 – 7.32 (2H, m, Ar), 7.31 – 7.19 (1H, m, Ar), 7.05 (2H, d, *J* 7, Ar), 5.32 (1H, d, *J* 7, 11-H), 4.40 (1H, d, *J* 8, 14-H), 4.27 (1H, td, *J* 11, 6, 20-*H*H), 4.17 (1H, td, *J* 11, 5, 20-H*H*), 2.39 (1H, ddd, *J* 13, 12, 6,

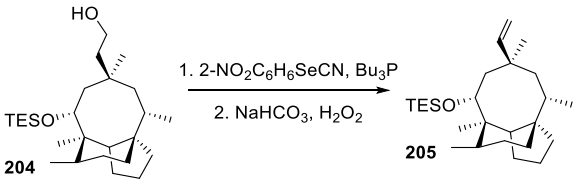
20-*H*H), 2.28 (1H, p, *J* 7, 10-*H*H), 2.11 (1H, dd, *J* 16, 9, 13-H*H*), 2.00 – 1.22 (13H, m), 1.20 (9H, s, COC*H*$_3$), 1.09 (3H, s, 18-H$_3$), 0.95 (9H, t, *J* 8, SiCH$_2$C*H*$_3$), 0.90 (3H, d, *J* 4, 16-H$_3$), 0.88 (3H, d, *J* 4, 17-H$_3$), 0.85 (3H, s, 15-H$_3$), 0.62 (6H, dd, *J* 16, 8, SiC*H*$_2$); δ_C (100 MHz, $CDCl_3$) 194.5 (CS) , 178.4 (CO), 153.4 , 129.6 , 126.5, 122.1, 90.1 (C-11), 68.1 (C-14), 62.1 (C-20), 47.9 (C-4), 47.5 (C-13), 45.7 (C-9), 42.5 (C-12), 41.2 (C-5), 38.7 (CO*C*CH$_3$), 36.0 (C-6), 35.2 (C-10), 34.8 (C-19), 34.0 (C-8), 29.4 (C-1), 28.2 (C-7), 27.4 (C-3), 27.3 (3-COC*C*H$_3$), 26.5 (C-18), 19.2 (C-2), 18.7 (C-16), 18.2 (C-15), 13.5 (C-17), 7.3 (SiCH$_2$*C*H$_3$), 6.4 (Si*C*H$_2$); Found (ESI) 681.4 [MNa$^+$] ($C_{38}H_{62}O_5SSiNa$ requires 681.3985).

Alcohol 204



To a solution of ester **202** (70 mg, 0.14 mmol) in CH_2Cl_2 (1.4 ml) was added DIBALH (21 µL, 0.21 ml) at −78 °C under N_2. The reaction mixture was stirred for 1 h and diluted with CH_2Cl_2 (2.8 ml). MeOH (3 drops) and saturated Rochelle salt solution (2.6 ml) were added. The mixture was stirred for 2 h and extracted with EtOAc (3 × 10 ml), dried over $MgSO_4$ and solvent evaporated *in vacuo* to give alcohol **204** as a colourless oil in a quantitative yield. ν_{max} (neat)/cm^{-1}: 3314, 2955, 2933, 2874, 1456; δ_H (400 MHz, $CDCl_3$) 4.41 (1H, d, *J* 9, 14-H), 3.77 (2H, dt, *J* 10, 6, 20-H$_2$), 2.25 (2H, ddd, *J* 13, 9, 6, 19-H$_2$), 1.94 (1H, dd, *J* 16, 9, 13-H*H*), 1.82 – 1.04 (15H, m), 0.97 (9H, t, *J* 8, SiCH$_2$C*H*$_3$), 0.92 (3H, s, 18-H$_3$), 0.89 (3H, d, *J* 7, 16-H$_3$), 0.84 (3H, s, 15-H$_3$), 0.80 (3H, d, *J* 7, 17-H$_3$), 0.65 (6H, q, *J* 9, 8, Si*CH*$_2$); δ_C (100 MHz, $CDCl_3$) 68.6 (C-14), 60.0 (C-20), 49.8 (C-13), 47.4 (C-4), 46.0 (C-12), 42.4 (C-5), 41.1 (C-3), 40.9 (C-19), 35.4 (C-6), 35.3 (C-9), 33.9 (C-8), 31.3 (C-18), 29.8 (C-10), 29.1 (C-1), 28.1 (C-7), 27.3 (C-3), 20.8 (C-17), 19.2 (C-2), 18.77 (C-16), 18.1 (C-15), 7.4 (SiCH$_2$*C*H$_3$), 6.5 (Si*C*H$_2$); Found (ESI) 445.3479 [MNa$^+$] ($C_{26}H_{50}O_2SiNa$ requires 445.3478).

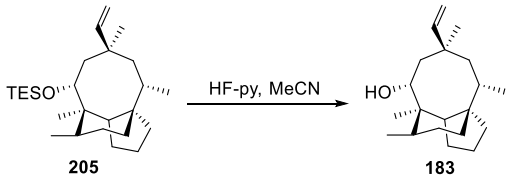
3-Deoxo-11-dehydroxy-14-methylsilyl mutilin 205



To a solution of alcohol **204** (15.0 mg, 35.5 µmol) in THF (0.4 ml) was added 2-$NO_2C_6H_6SeCN$ (20.1 mg, 88.7 µmol) and Bu_3P (17.9 mg, 88.7 µmol). After stirring for 1.5 h at room temperature, $NaHCO_3$ (20 mg, 0.23 mmol) and H_2O_2 (0.05 ml) were added at 0 °C. The reaction mixture was

stirred for 14 h at 0 °C and saturated solution of NH_4Cl (2 ml) was added. The mixture was extracted with Et_2O (4x 20 ml) and the organic layers were washed with saturated solution of $NaHCO_3$ (10 ml) and brine (10 ml), were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The residue was purified by silica gel column chromatography using hexane to give silyl ester **205** as a colourless oil (7.1 mg, 50%). ν_{max} (neat)/cm^{-1}: 2956, 2921, 2874 , 1456; δ_H (400 MHz, $CDCl_3$) 6.12 (1H, dd, *J* 18, 11, 19-H), 5.13 – 5.09 (1H, dd, *J* 18, 1, 20-*H*H), 5.07 (1H, dd, *J* 11, 1, 20-H*H*), 4.31 (1H, d, *J* 8, 14-H), 2.03 (1H, dd, *J* 15, 8, 13-H*H*), 1.91 – 1.07 (16H, m), 0.95 (9H, m, $SiCH_2CH_3$), 0.94 (3H, s, 18-H_3), 0.87 (3H, d, *J* 7, 16-H_3), 0.84 (3H, s, 15-H_3), 0.82 (d, *J* 7, 17-H_3), 0.68 – 0.60 (6H, m, $SiCH_2$); δ_C (100 MHz, $CDCl_3$) 147.5 (C-19), 112.2 (C-20), 69.6 (C-14), 48.3 (C-13), 47.5 (C-4), 46.0 (C-12), 42.3 (C-5), 41.9 (C-11), 40.1 (C-9), 35.3 (C-6), 33.9 (C-8), 32.4 (C-18), 30.4 (C-10), 29.2 (C-1), 28.1 (C-7), 27.3 (C-3), 20.9 (C-17), 19.2 (C-2), 18. 8 (C-16), 18.1 (C-15), 7.3 ($SiCH_2CH_3$), 6.3 ($SiCH_2$); Found (EI) 404.3468 [M] ($C_{26}H_{48}OSi$ requires 404.3474).

3-Deoxo-11-dehydroxy-mutilin 183



205 183

To a solution of silyl ester **205** in MeCN was added HF-pyridine (1 drop). After the mixture reaction was stirred for 2 h, a saturated solution of $NaHCO_3$ (2 drops) was added. The mixture was extracted with EtOAc (4 × 2 ml). The organic layers were dried over $MgSO_4$ and solvent evaporated *in vacuo*. The residue was purified by column chromatography using 10% EtOAc in hexane to give alcohol 3-deoxo-11-dehydroxy-mutilin **183** as a colourless oil (3.0 mg, 43%). ν_{max} (neat)/cm^{-1}: 3486, 2956, 2924, 2863, 1456; δ_H (400 MHz, $CDCl_3$) 5.84 (1H, dd, *J* 18, 11, 19-H), 5.21 (1H, dd, *J* 18, 1, 20-*H*H), 5.11 (1H, dd, *J* 11, 1, 20-H*H*), 4.22 (1H, d, *J* 8,14-H), 2.00 (1H, dd, *J* 15, 8, 13-H*H*), 1.83 – 1.63 (5H, m, 3-H_2,4-H,10-H,6-H), 1.62 – 1.52 (1H, m, 2-H*H*), 1.51 – 1.06 (9H, m, 7-H_2,8-H_2,1-H_2,11-H*H*,13-*H*H, 2-*H*H), 1.02 (1H, d, *J* 7, 11-*H*H), 0.96 (3H, d, *J* 7, 16-H_3), 0.96 (3H, s, 18-H_3), 0.86 (3H, s, 15-H_3), 0.81 (3H, d, *J* 7, 17-H_3); δ_C (100 MHz, $CDCl_3$) 147.2 (C-19), 112.9 (C-20), 69.0 (C-14), 47.8 (C-4), 46.3 (C-13), 45.9 (C-12), 43.2 (C-11), 41.3 (C-5), 40.6 (C-9), 35.0 (C-6), 33.9 (C-8), 33.1 (C-18), 31.1 (C-10), 28.7 (C-1), 28.0 (C-7), 27.1 (C-3), 21.3 (C-17), 19.0 (C-2), 18.5 (C-6), 17.3 (C-15); Found (CI) 291.2681 [MH^+] ($C_{20}H_{35}O$ requires 291.2682).

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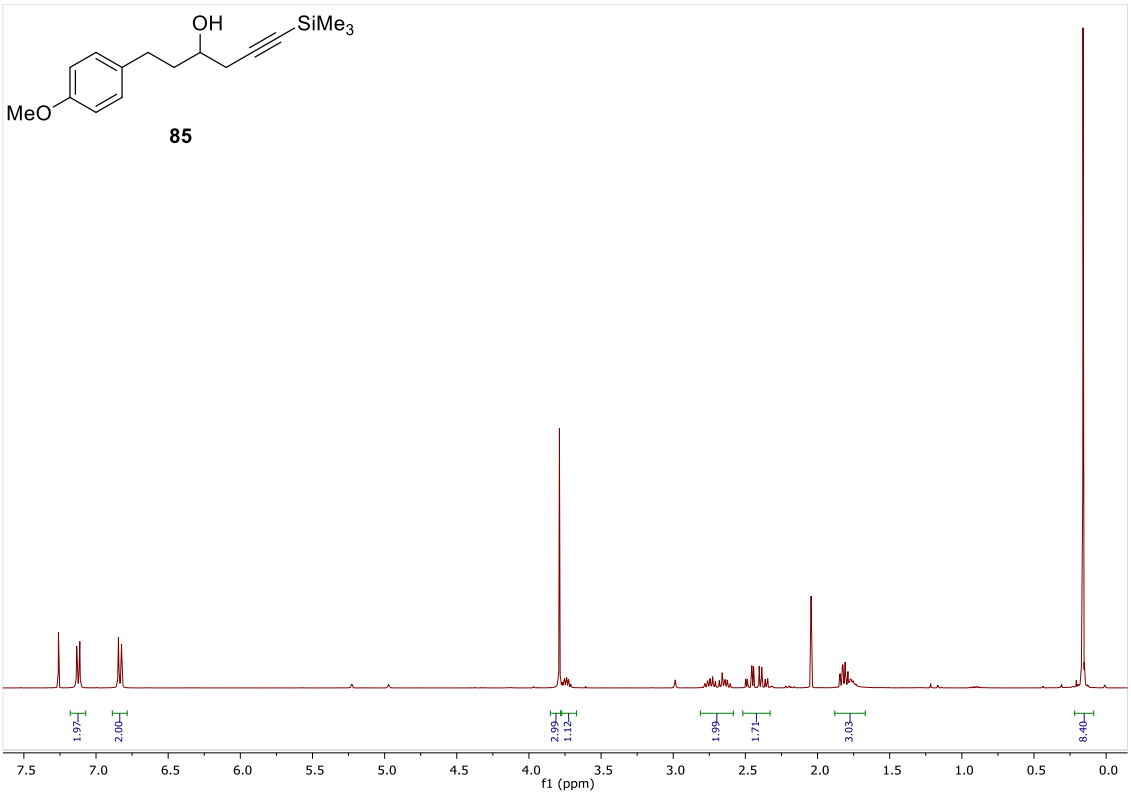
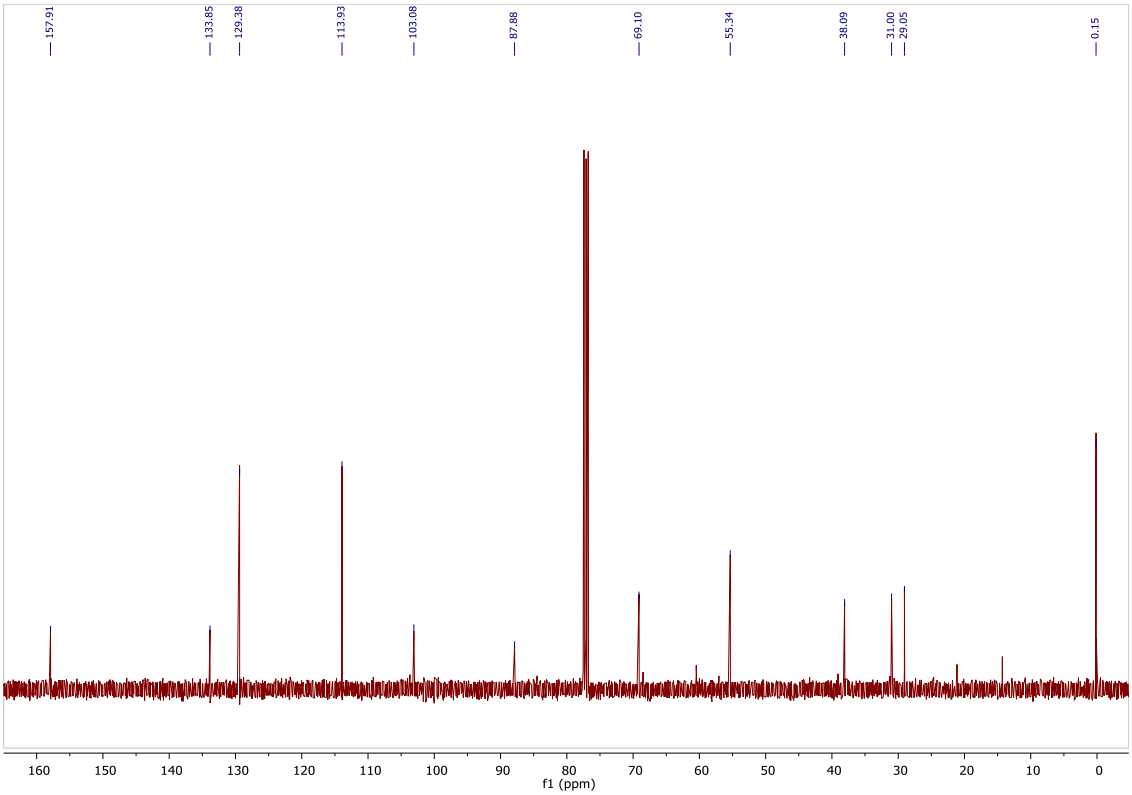
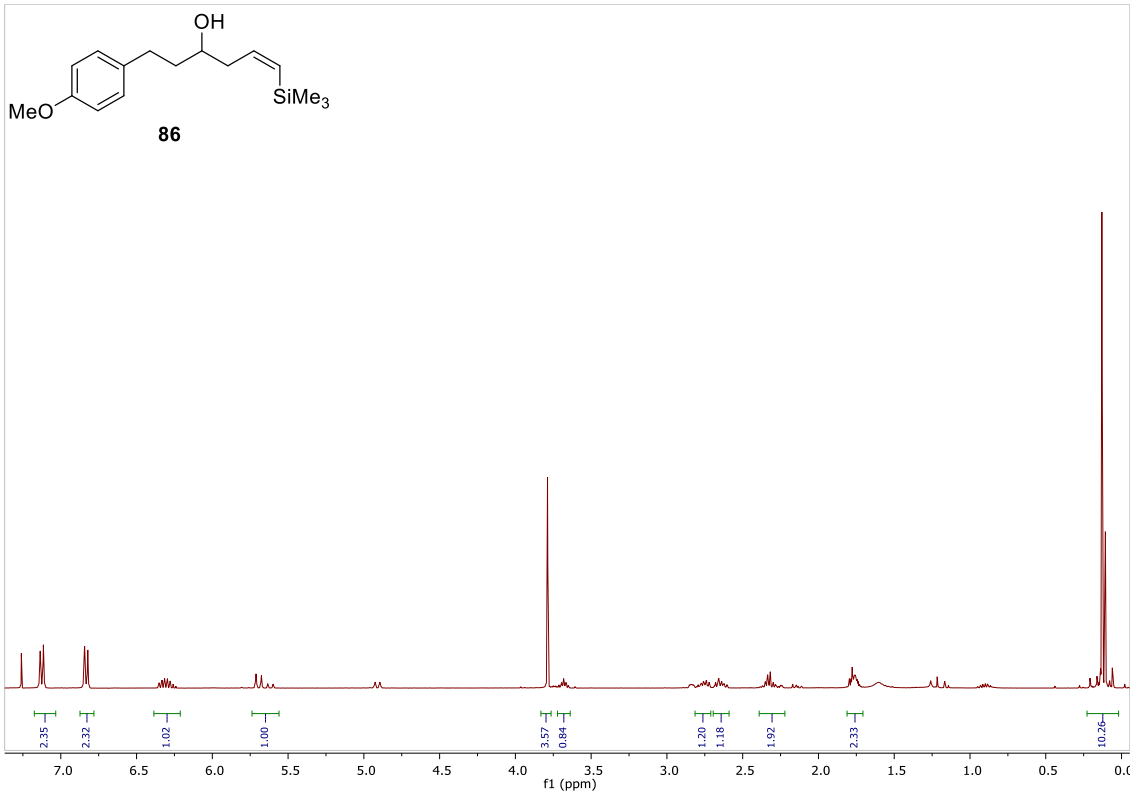
5. NMR Spectra

5.1 NMR Spectra pertaining to chapter 1



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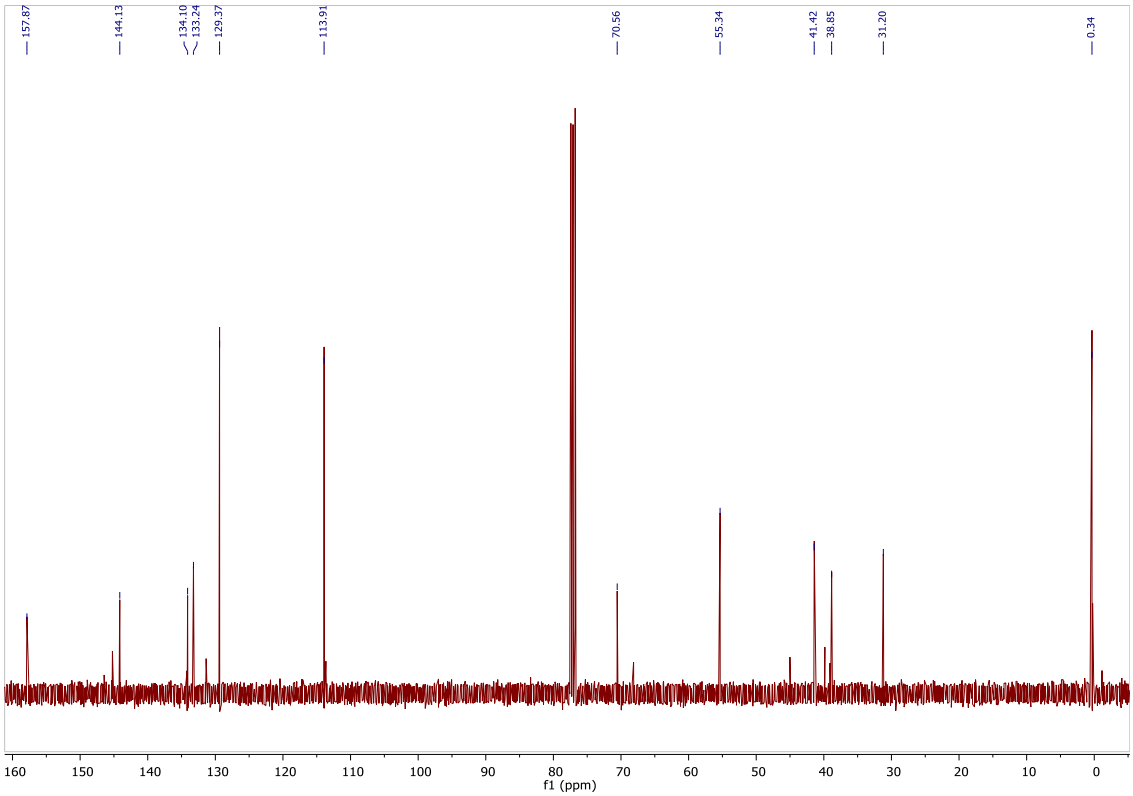
MeO
SiMe3
86
2.35
2.32
1.02
1.00
3.57
0.84
1.20
1.18
1.92
2.33
10.26
f1 (ppm)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144.13
134.10
133.24
129.37
113.91
70.56
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38.85
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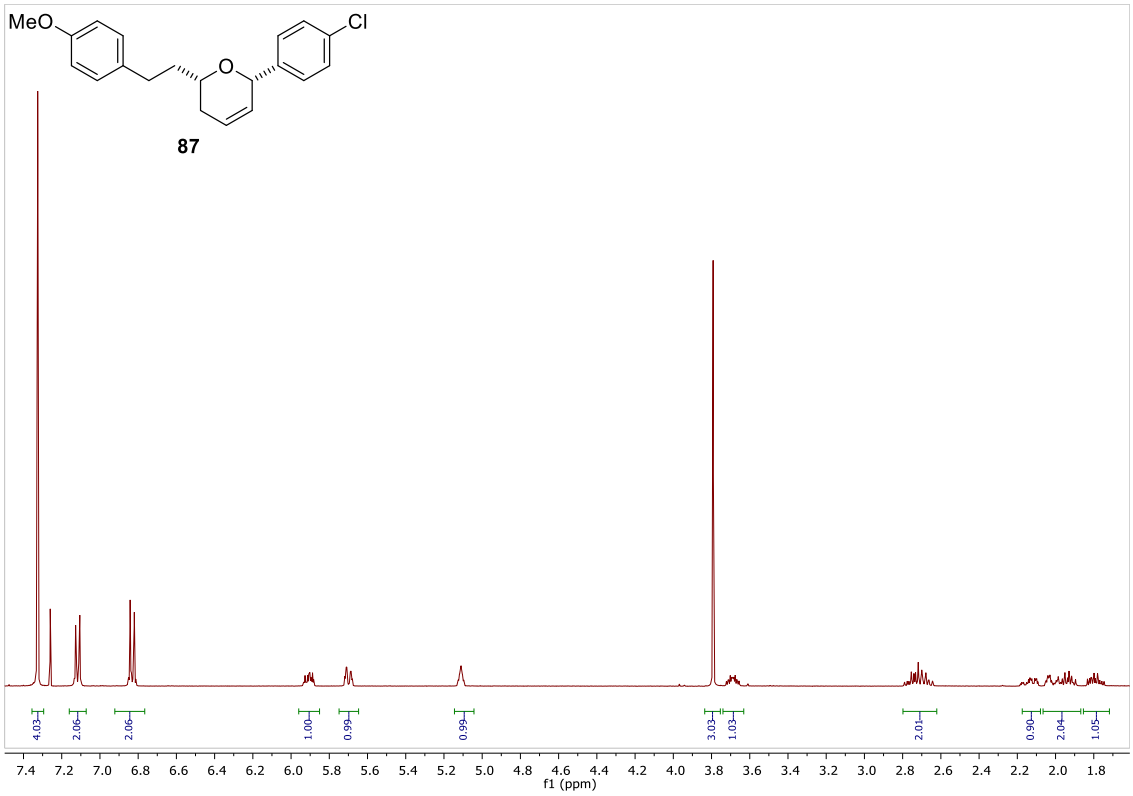
0.34
f1 (ppm)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Cl
O
87
4.03
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2.06
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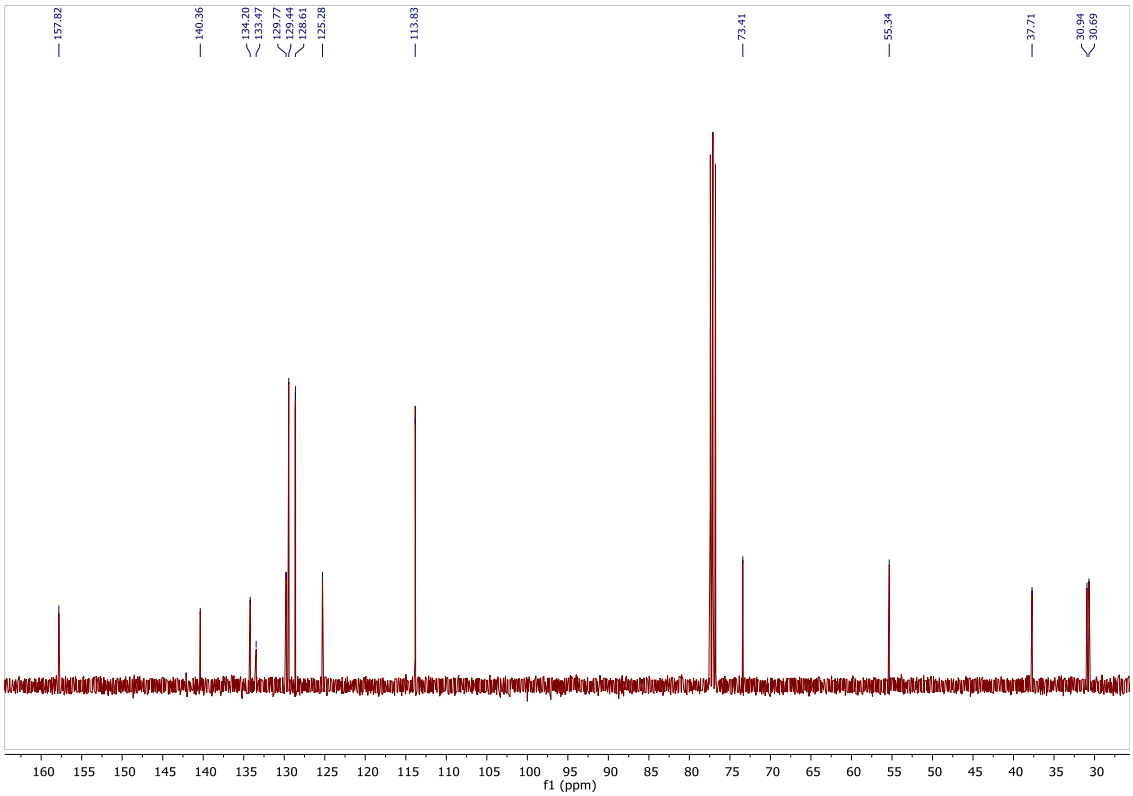
0.99
3.03
1.03
2.01
0.90
2.04
1.05
f1 (ppm)


157.82
140.36
134.20
133.47
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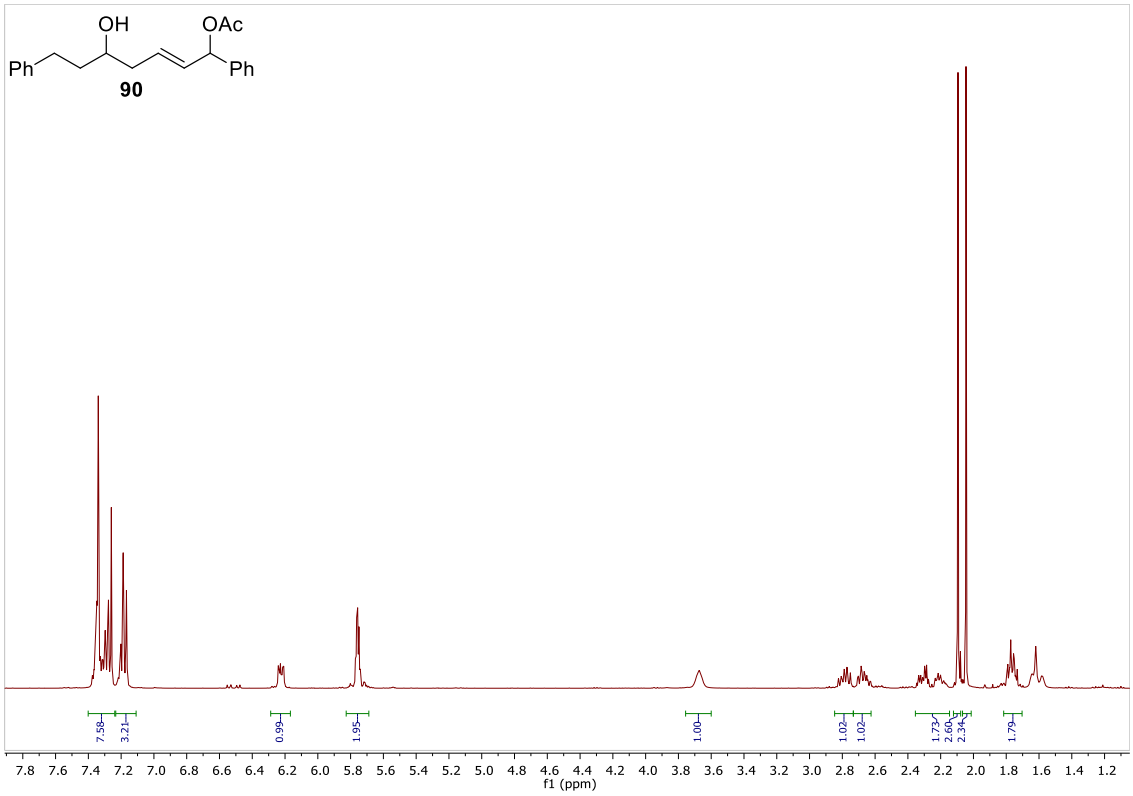
128.61
125.28
113.83
73.41
55.34
37.71
30.94
30.69
f1 (ppm)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OAc
Ph
Ph
90
7.58
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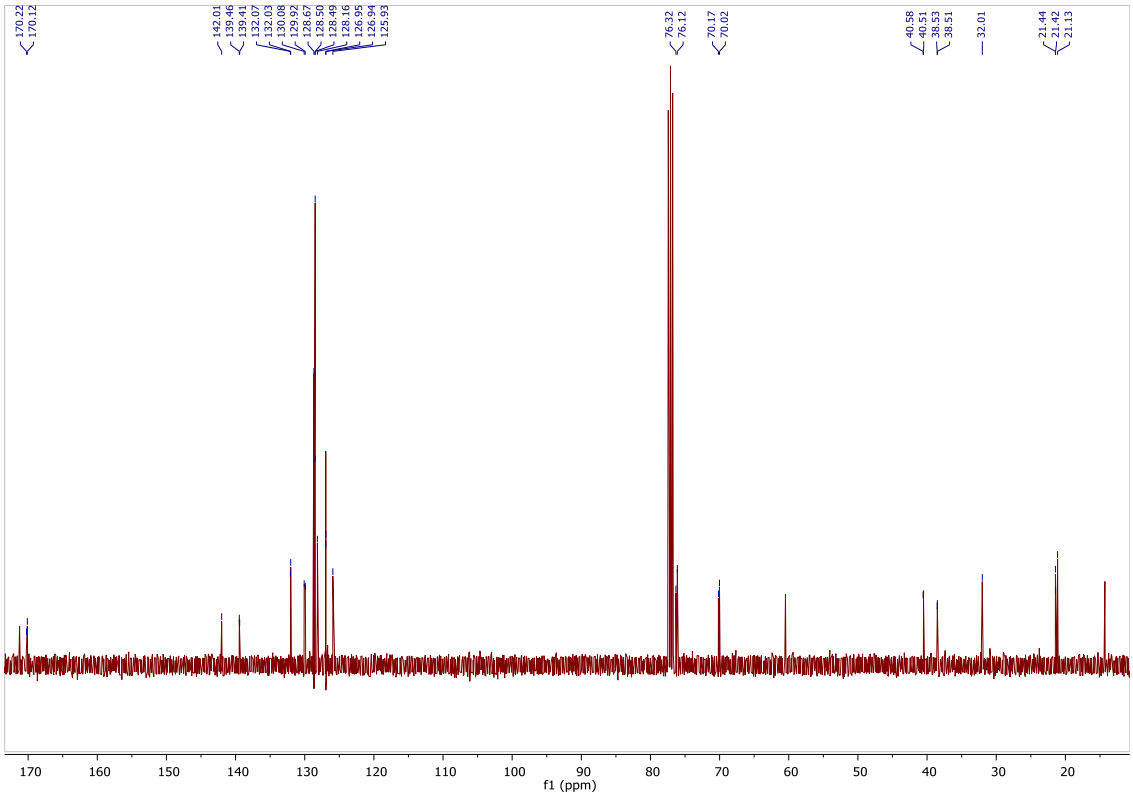
1.00
1.02
1.02
1.73
2.60
2.94
1.79
f1 (ppm)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142.01
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139.41
132.07
132.03
130.08
129.92
128.67
128.50
128.49
128.16
126.95
126.94
125.93
76.32
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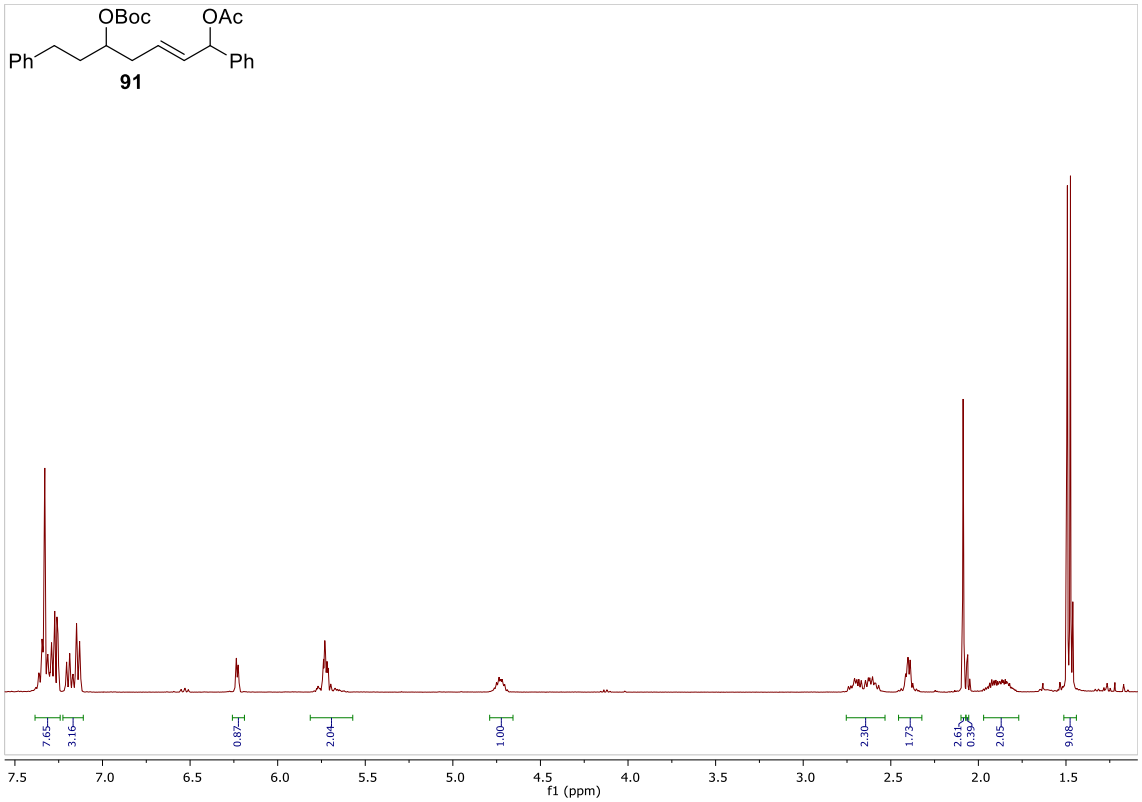
32.01
21.44
21.42
21.13
f1 (ppm)


OBoc
OAc
Ph
Ph
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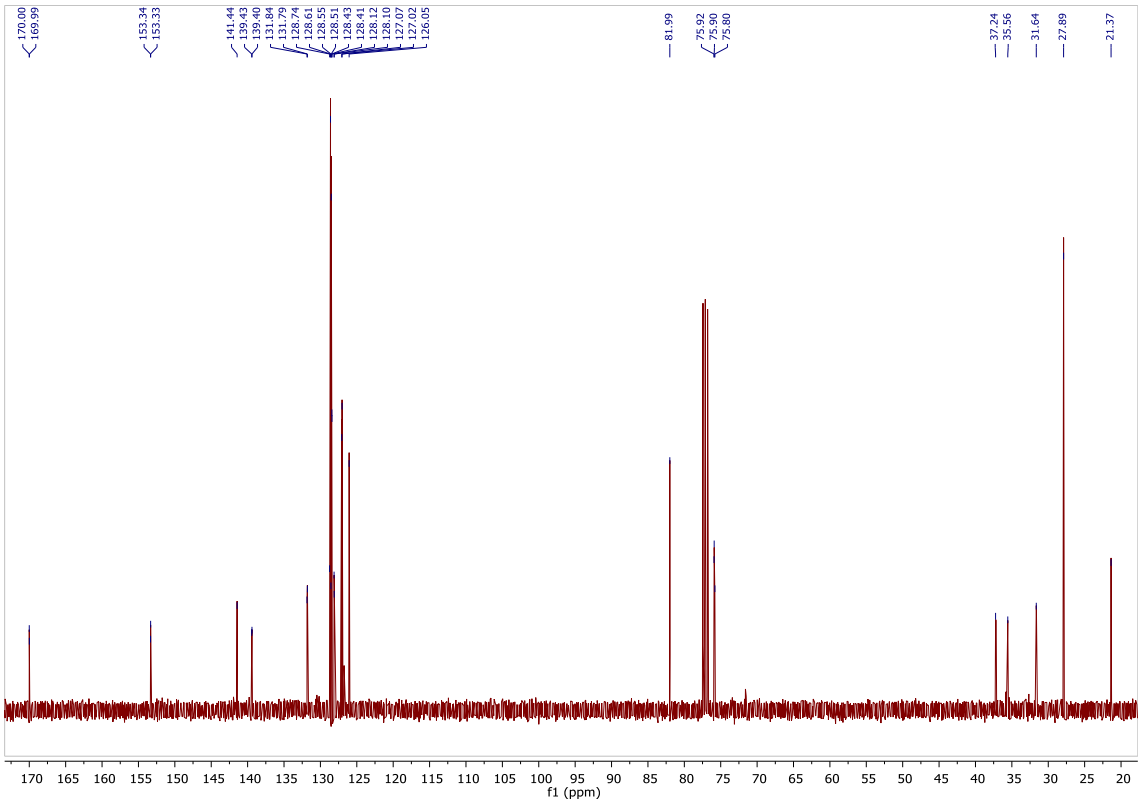
9.08
f1 (ppm)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153.33
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139.43
139.40
131.84
131.79
128.74
128.61
128.55
128.51
128.43
128.41
128.12
128.10
127.07
127.02
126.05
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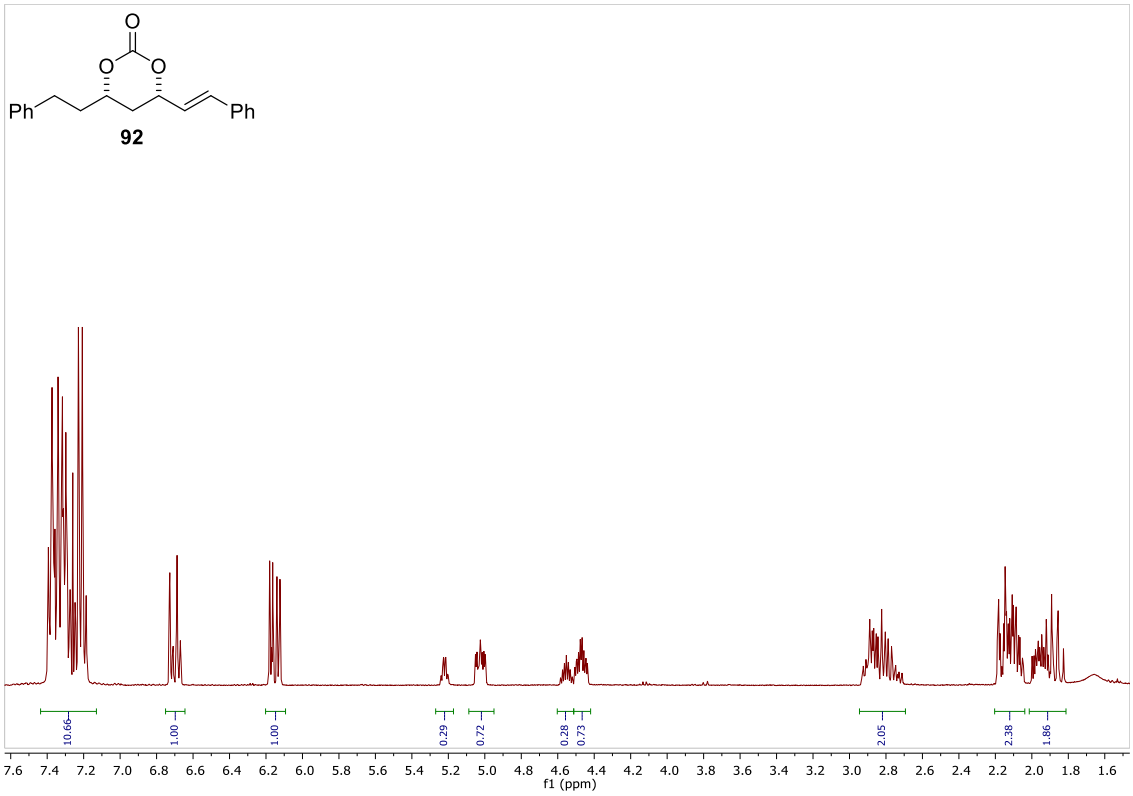
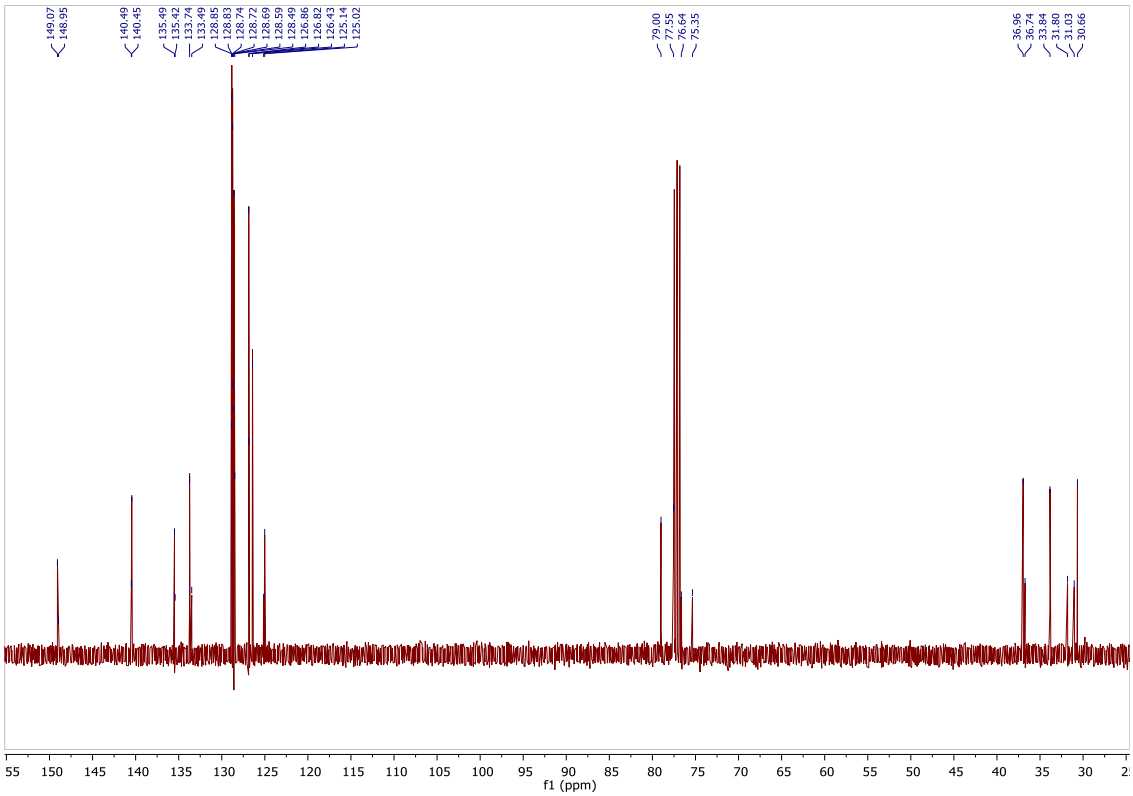
75.90
75.80
37.24
35.56
31.64
27.89
21.37
f1 (ppm)


O
O
O
Ph
Ph
92
10.66
1.00
1.00
0.29
0.72
0.28
0.73
2.05
2.38
1.86
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)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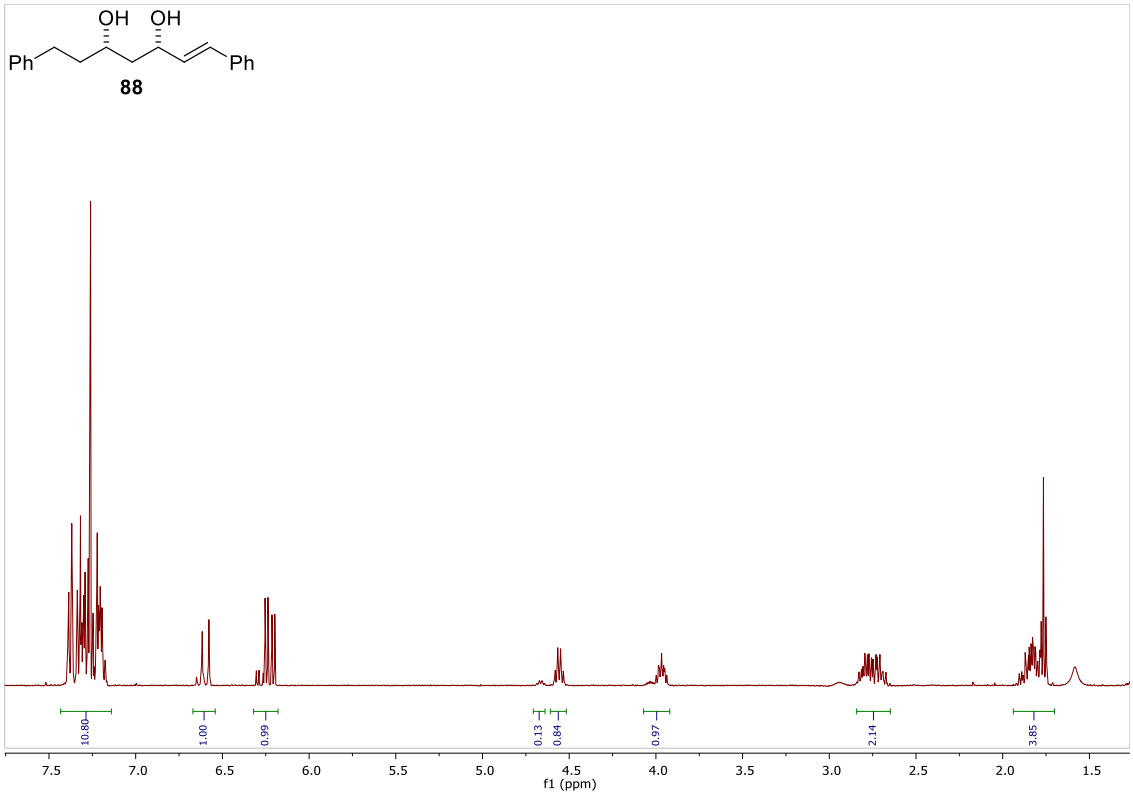
133.49
128.85
128.83
128.74
128.72
128.69
128.59
128.49
126.86
126.82
126.43
125.14
125.02
79.00
77.55
75.64
75.35
36.96
36.74
33.84
31.80
31.03
30.66
55 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30
f1 (ppm)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0.84
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2.14
3.85
7.5
7.0
6.5
6.0
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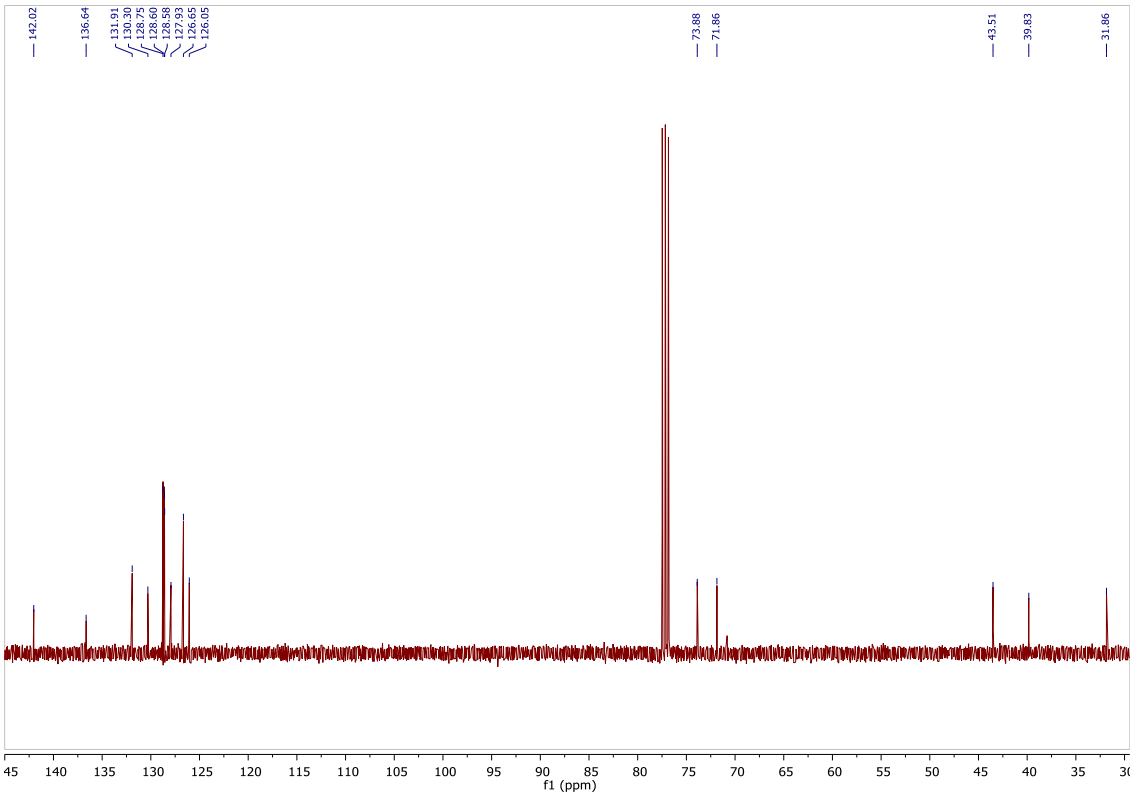
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)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128.58
127.93
126.65
126.05
73.88
71.86
43.51
39.83
31.86
45
140
135
130
125
120
115
110
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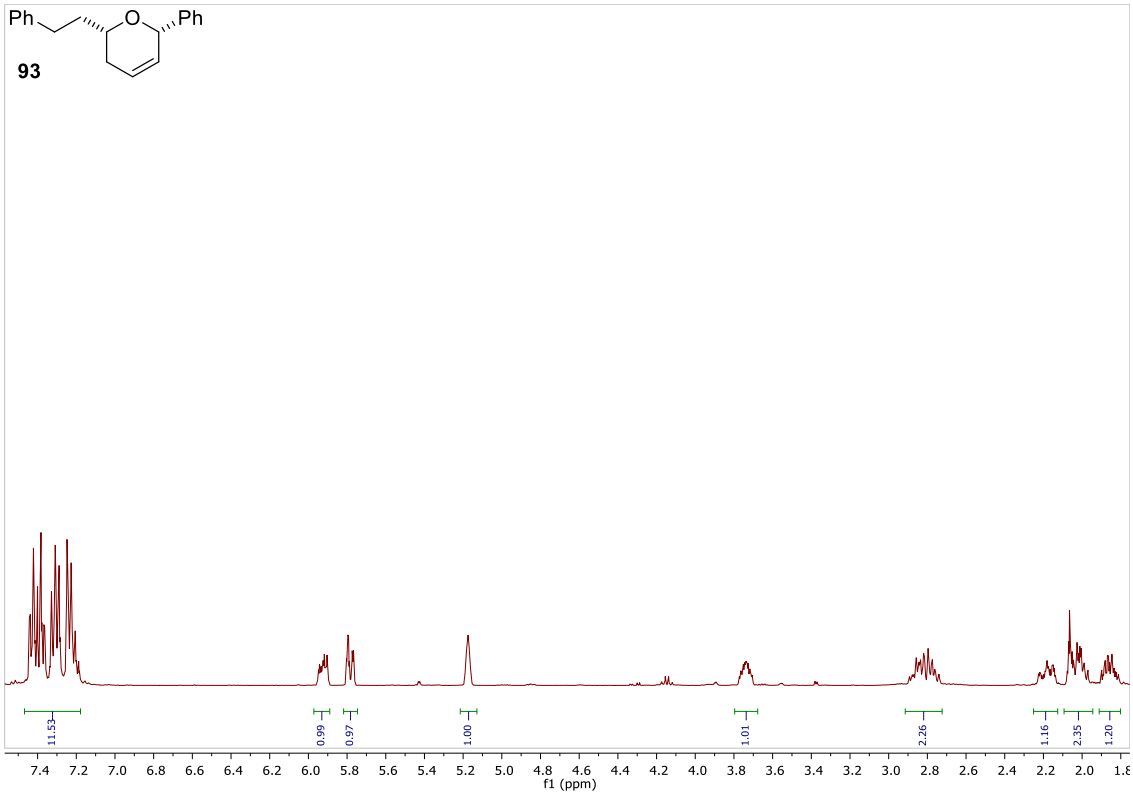
100
95
90
85
80
75
70
65
60
55
50
45
40
35
f1 (ppm)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2.26
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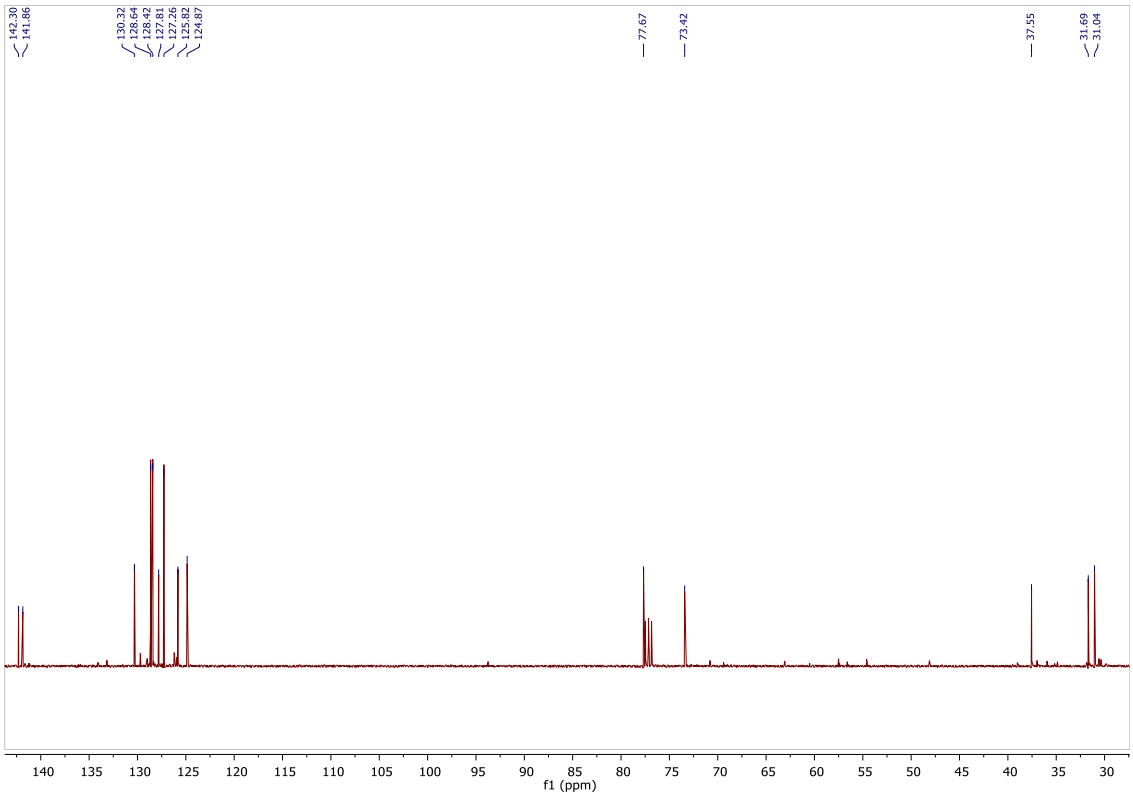
2.35
1.20
f1 (ppm)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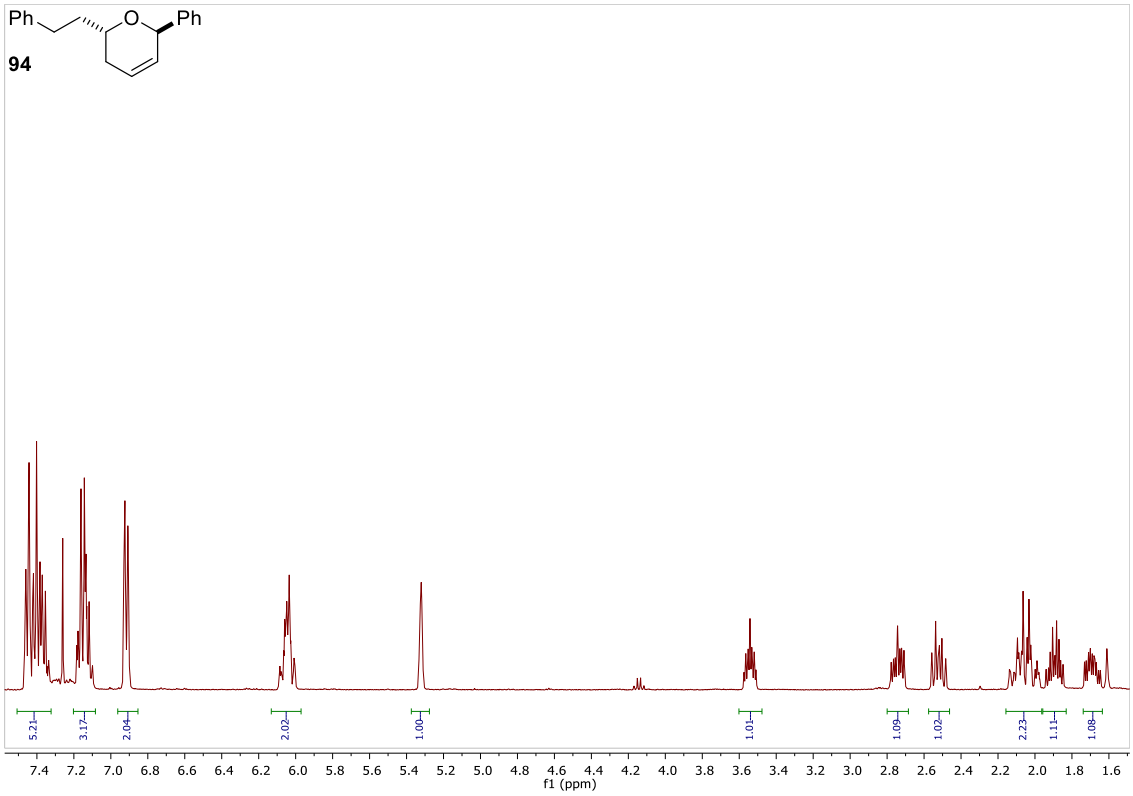
37.55
31.69
31.04
f1 (ppm)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O
Ph
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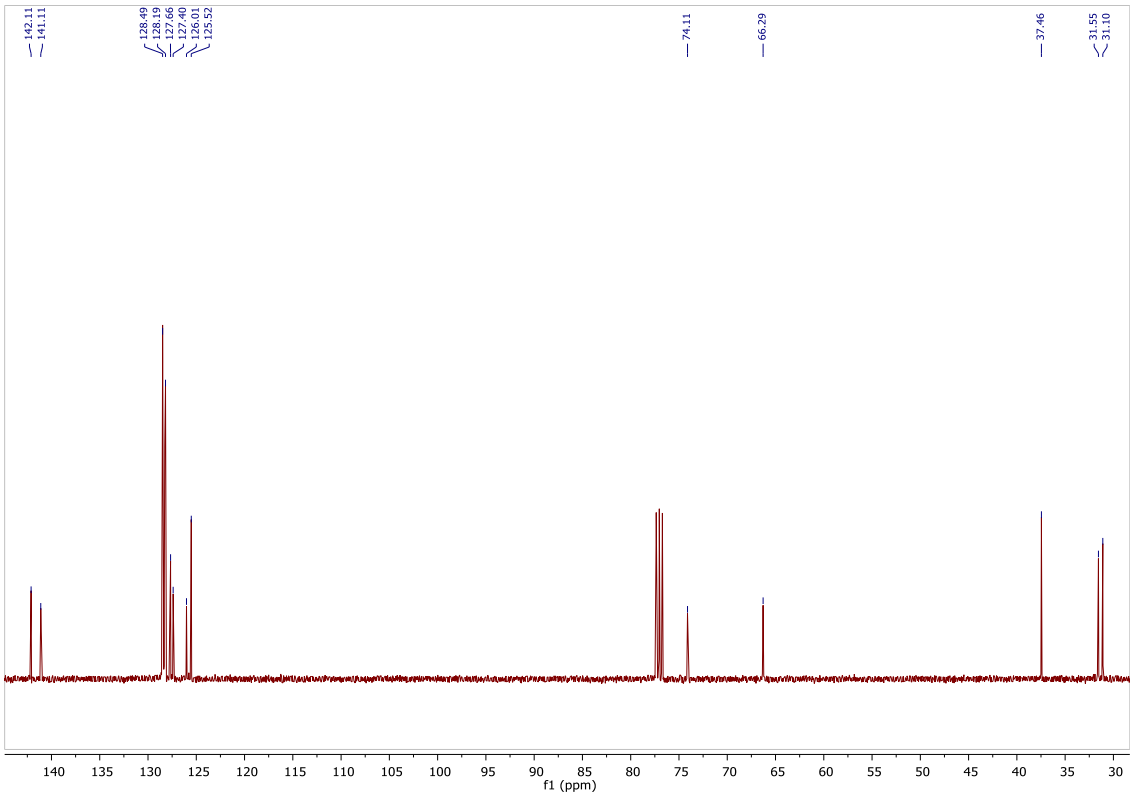
5.21
3.17
2.04
2.02
1.00
1.01
1.09
1.02
2.23
1.11
1.08
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)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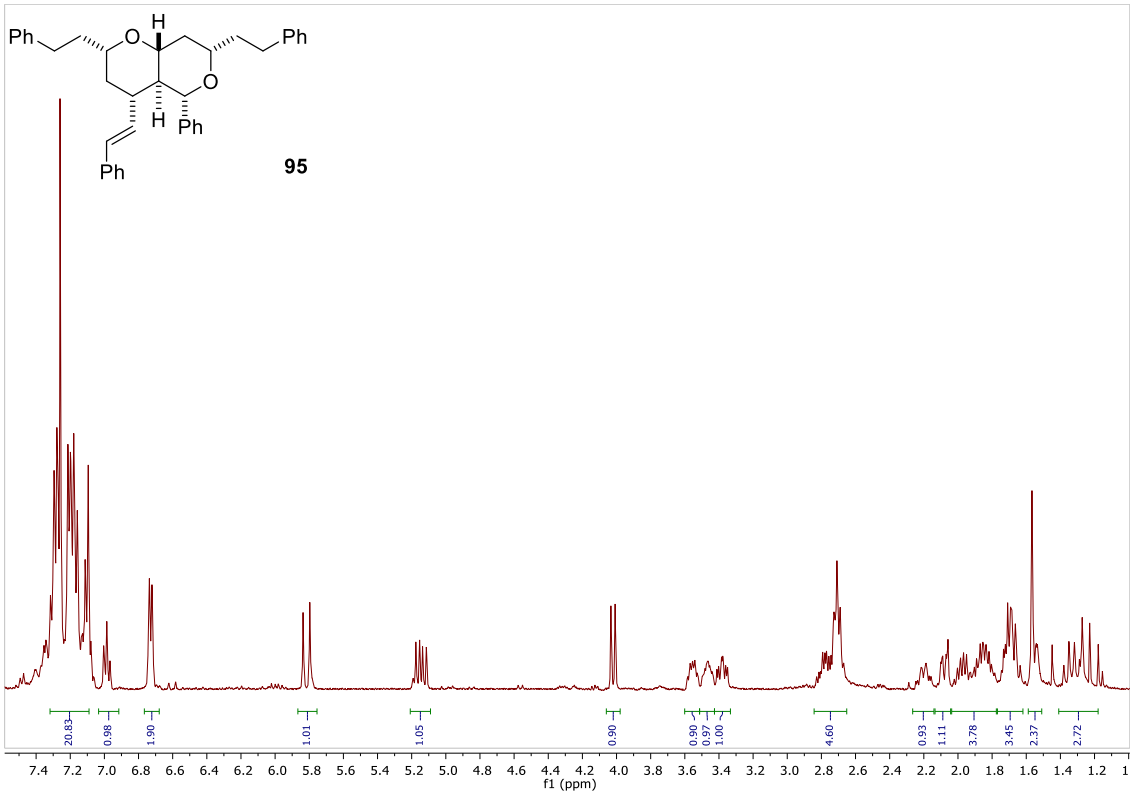
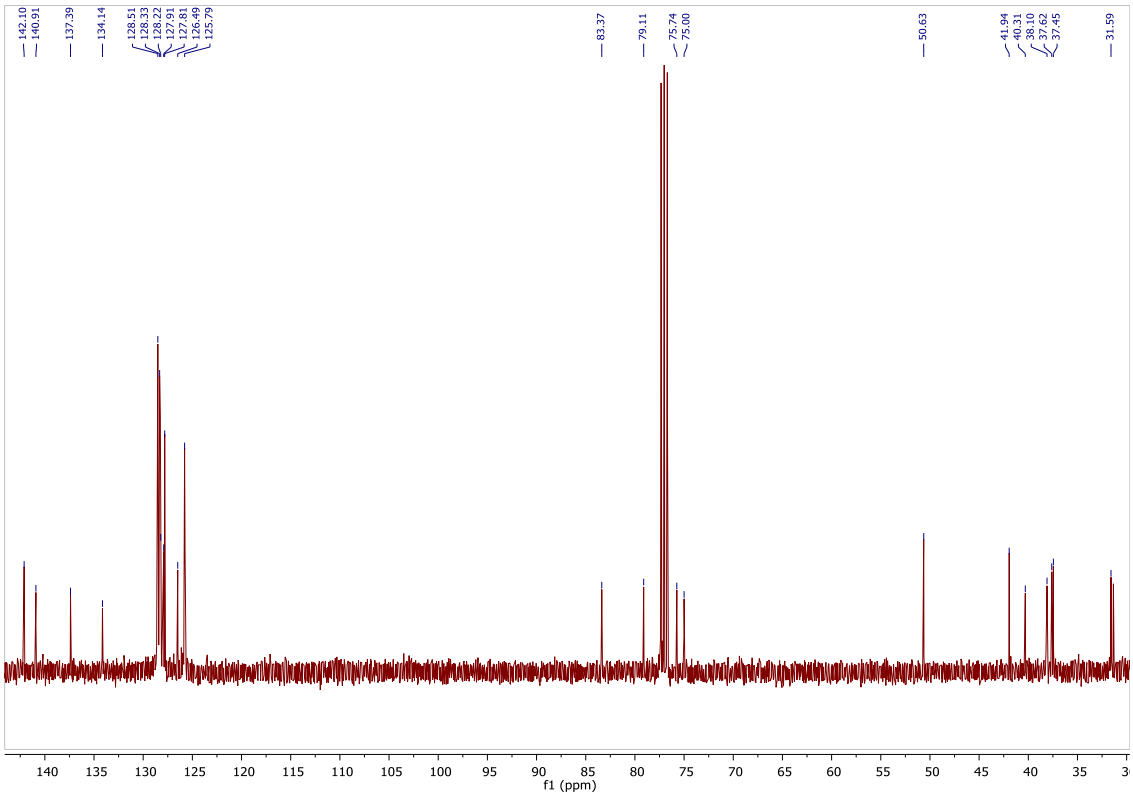
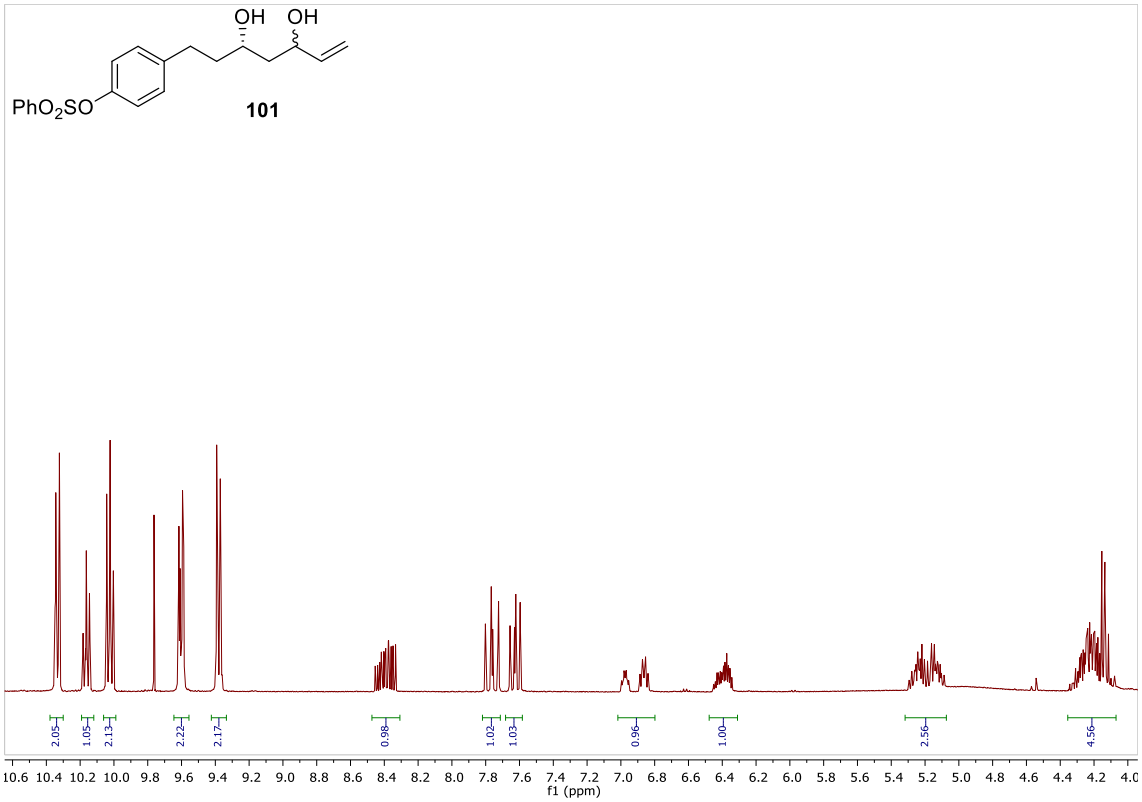
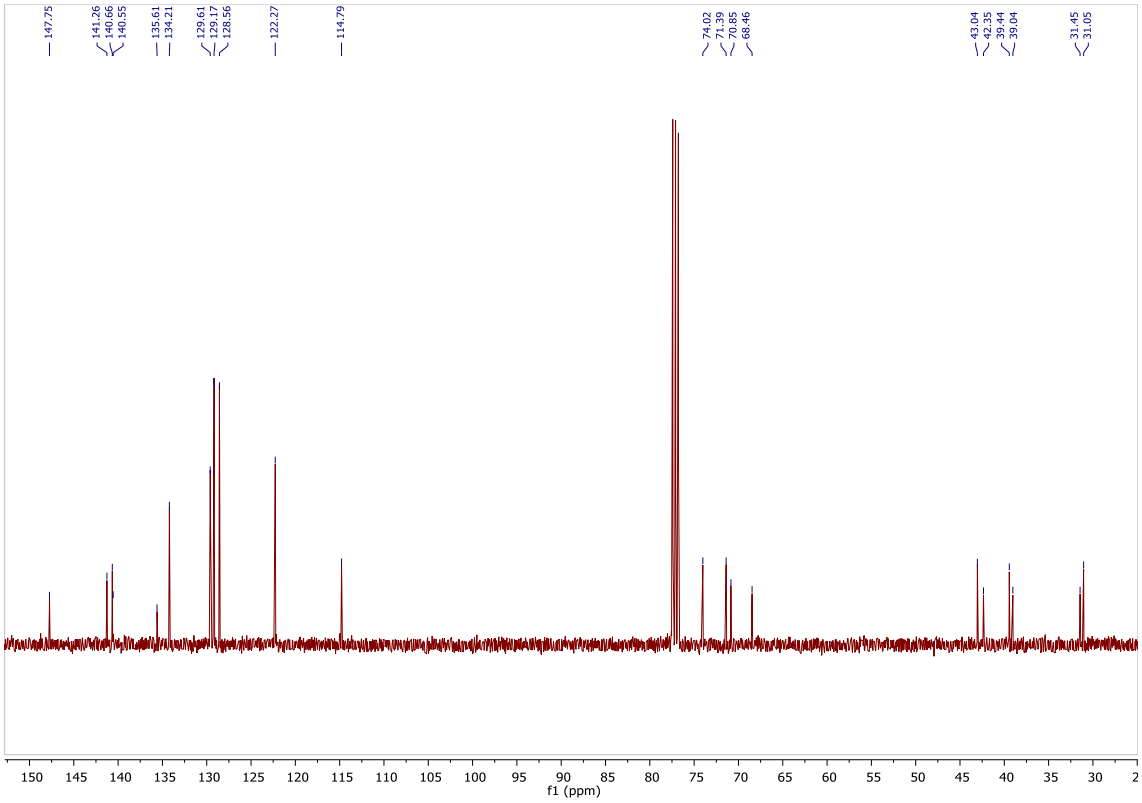
126.01
125.52
74.11
66.29
37.46
31.55
31.10
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30
f1 (ppm)


Ph
O
H
Ph
O
H
Ph
Ph
95
20.83
0.98
1.90
1.01
1.05
0.90
0.90
0.97
1.00
4.60
0.93
1.11
3.78
3.45
2.37
2.72
f1 (ppm)


142.10
140.91
137.39
134.14
128.51
128.33
128.22
127.91
127.81
126.49
125.79
83.37
79.11
75.74
75.00
50.63
41.94
40.31
38.10
37.62
37.45
31.59
f1 (ppm)


OH
OH
PhO2SO
101
2.05
1.05
2.13
2.22
2.17
0.98
1.02
1.03
0.96
1.00
2.56
4.56
f1 (ppm)


147.75
141.26
140.66
140.55
135.61
134.21
129.61
129.17
128.56
122.27
114.79
74.02
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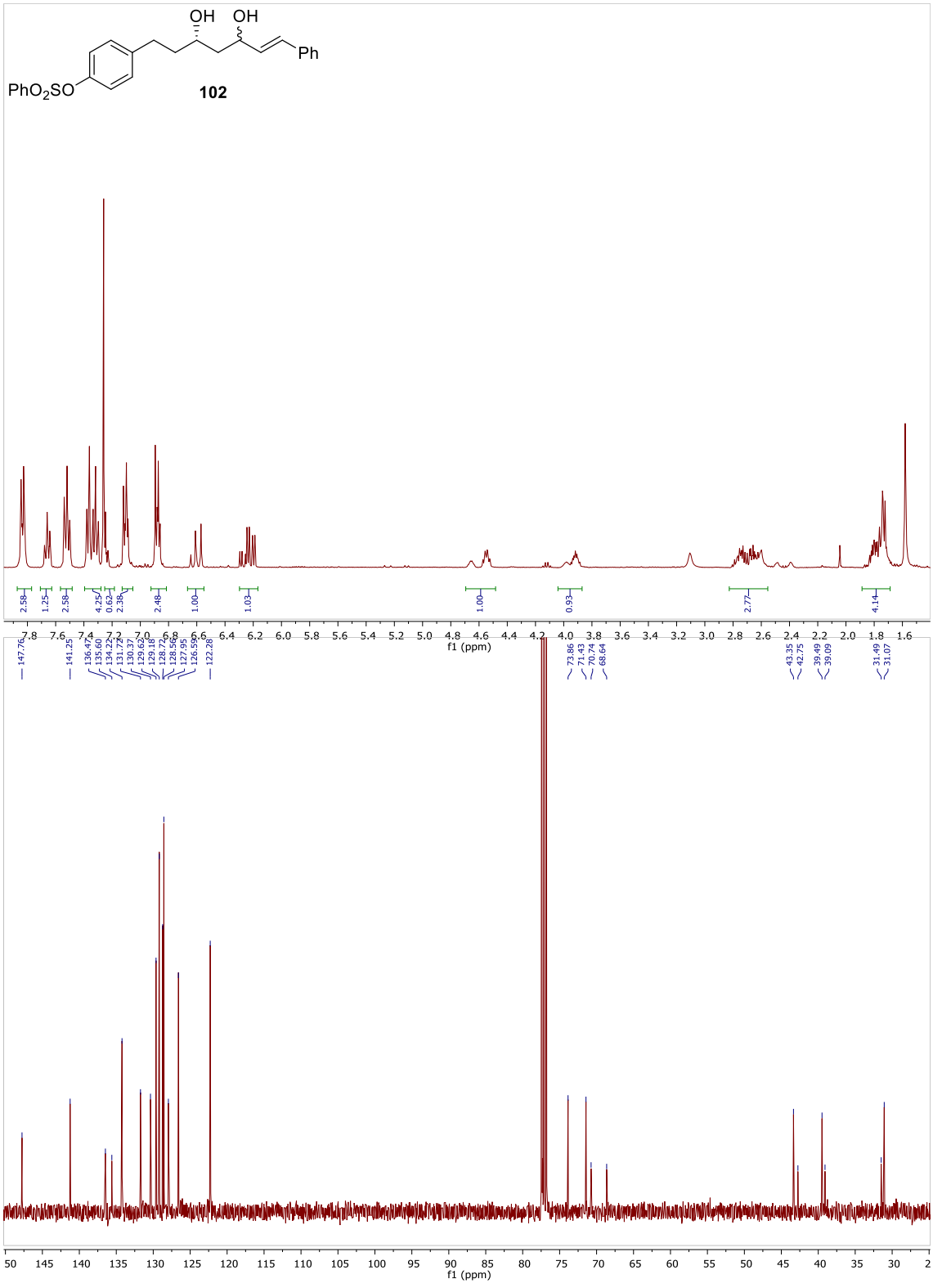
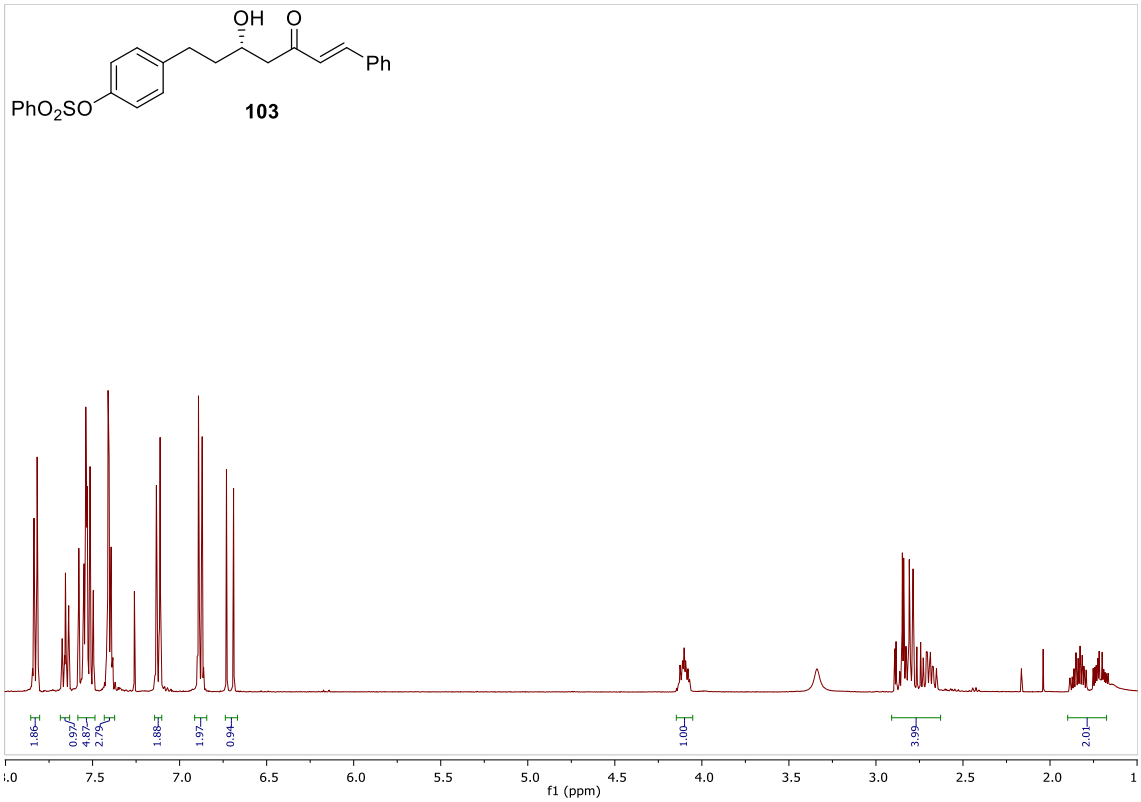
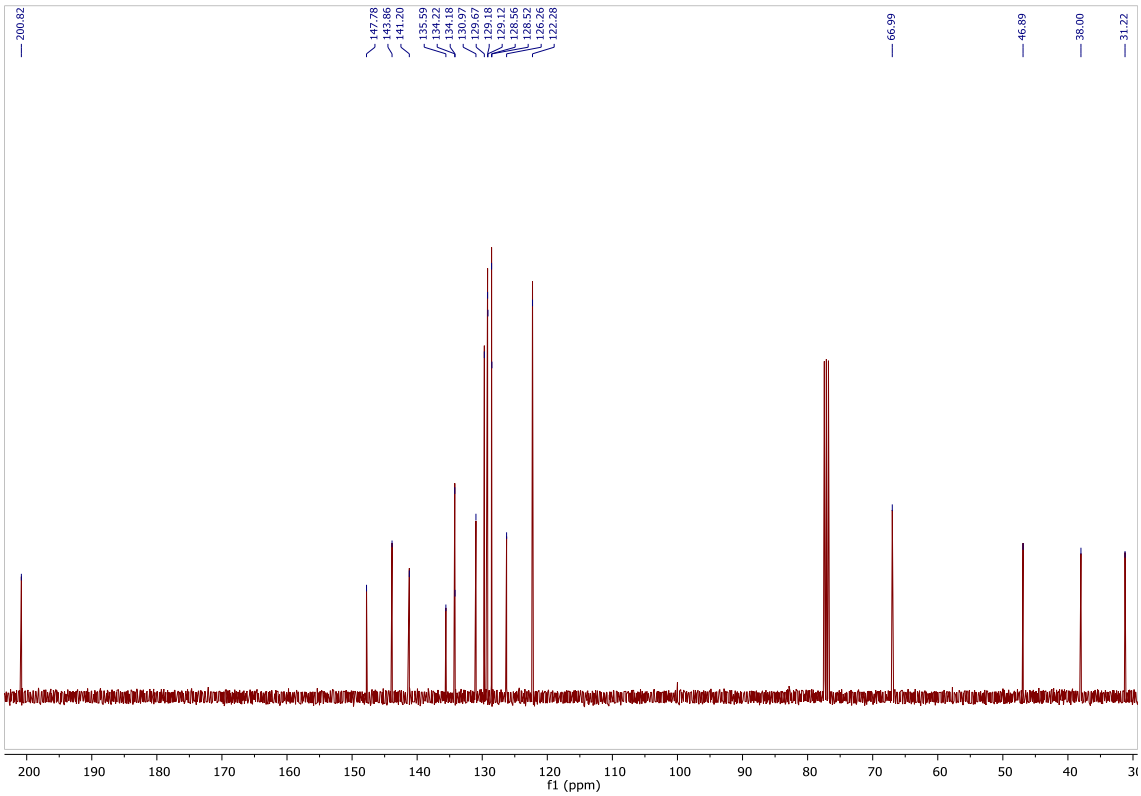
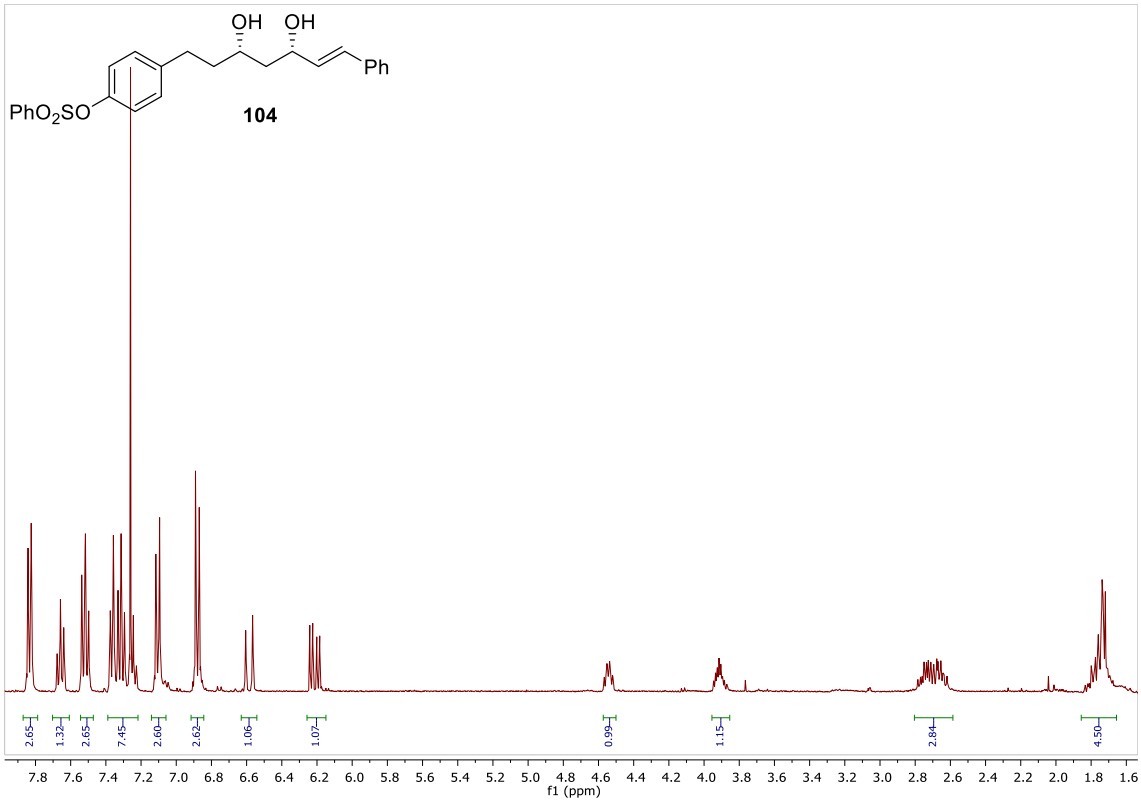
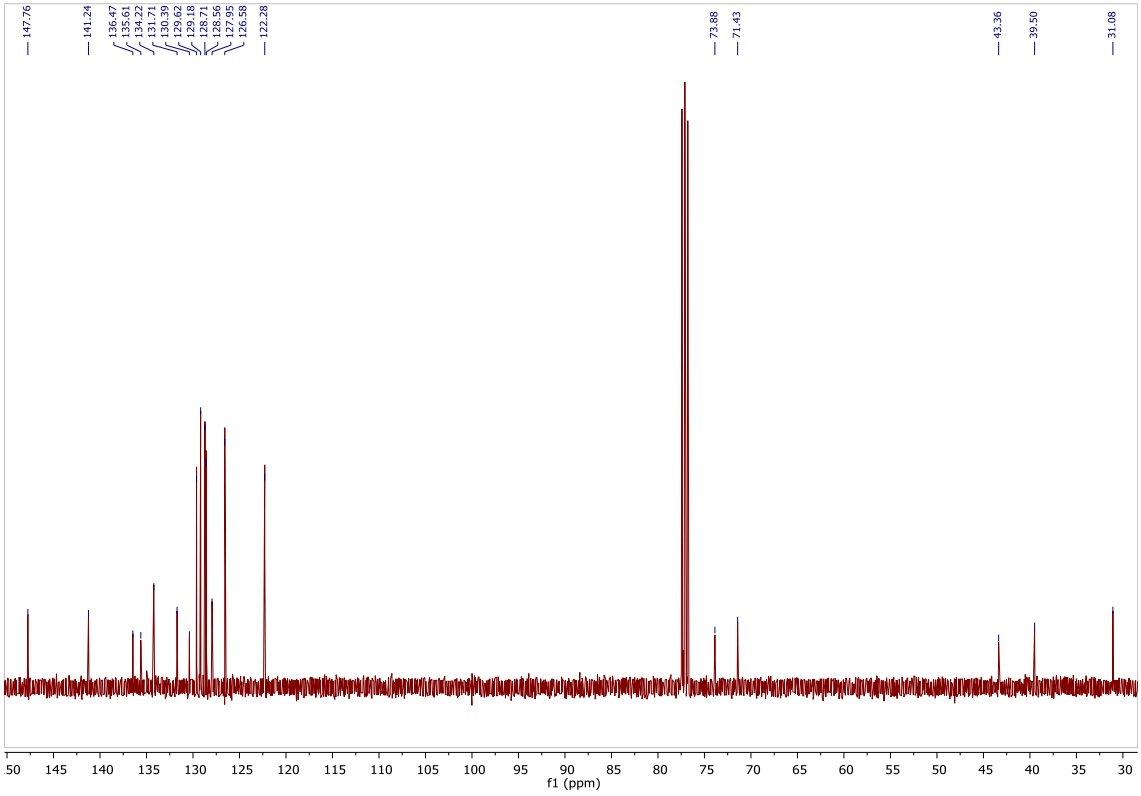
70.85
68.46
43.04
42.35
39.44
39.04
31.45
31.05
f1 (ppm)

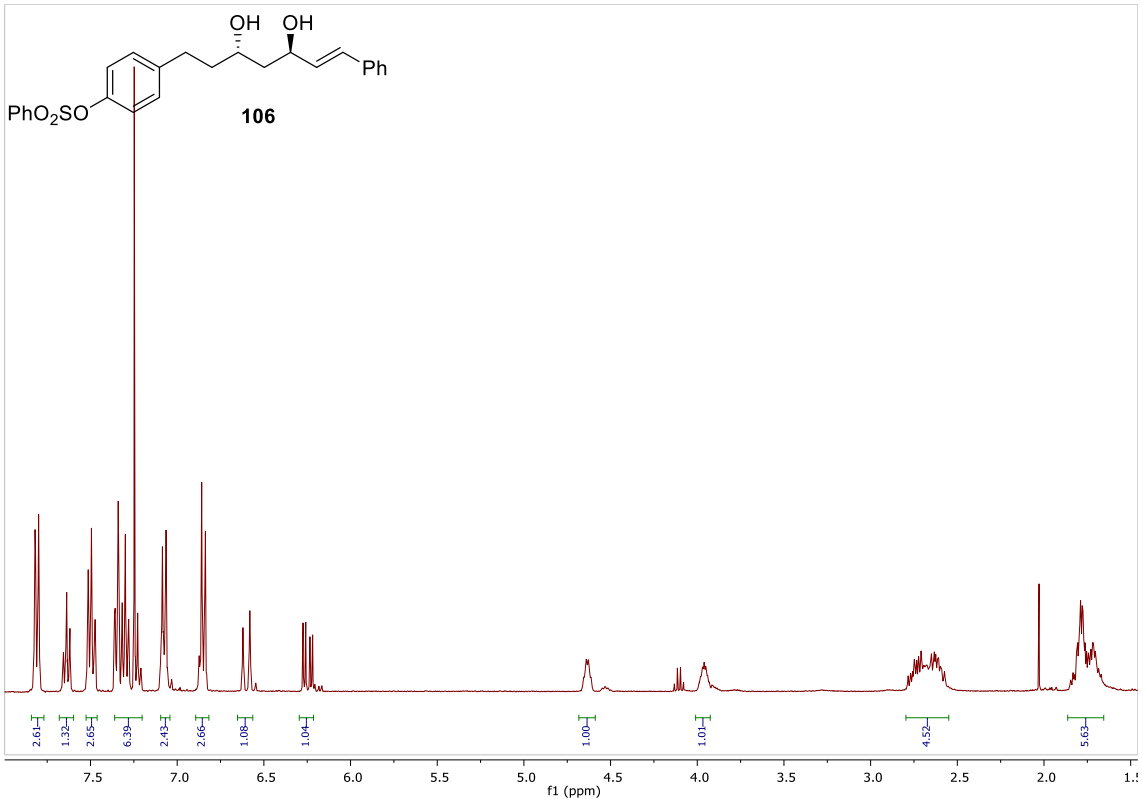

OH
OH
Ph
PhO2SO
102
f1 (ppm)
f1 (ppm)

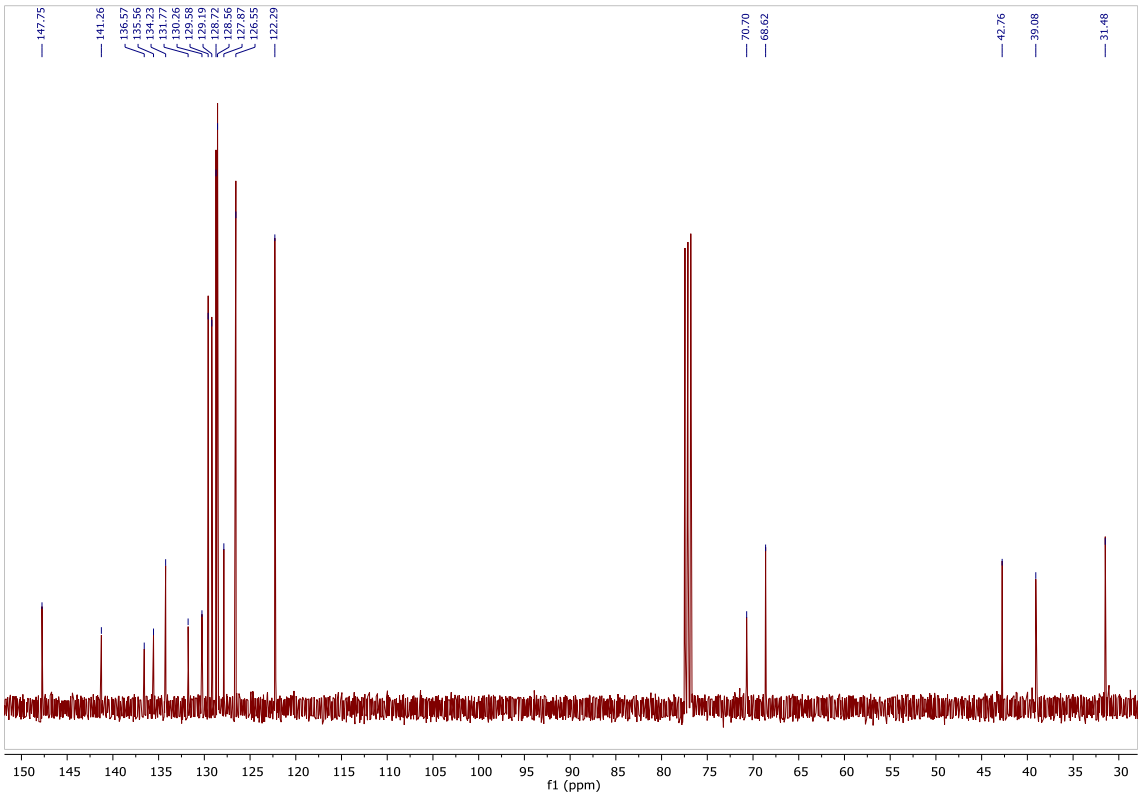

OH
O
Ph
PhO2SO
103
1.86
0.97
4.87
2.79
1.88
1.97
0.94
1.00
3.99
2.01
f1 (ppm)

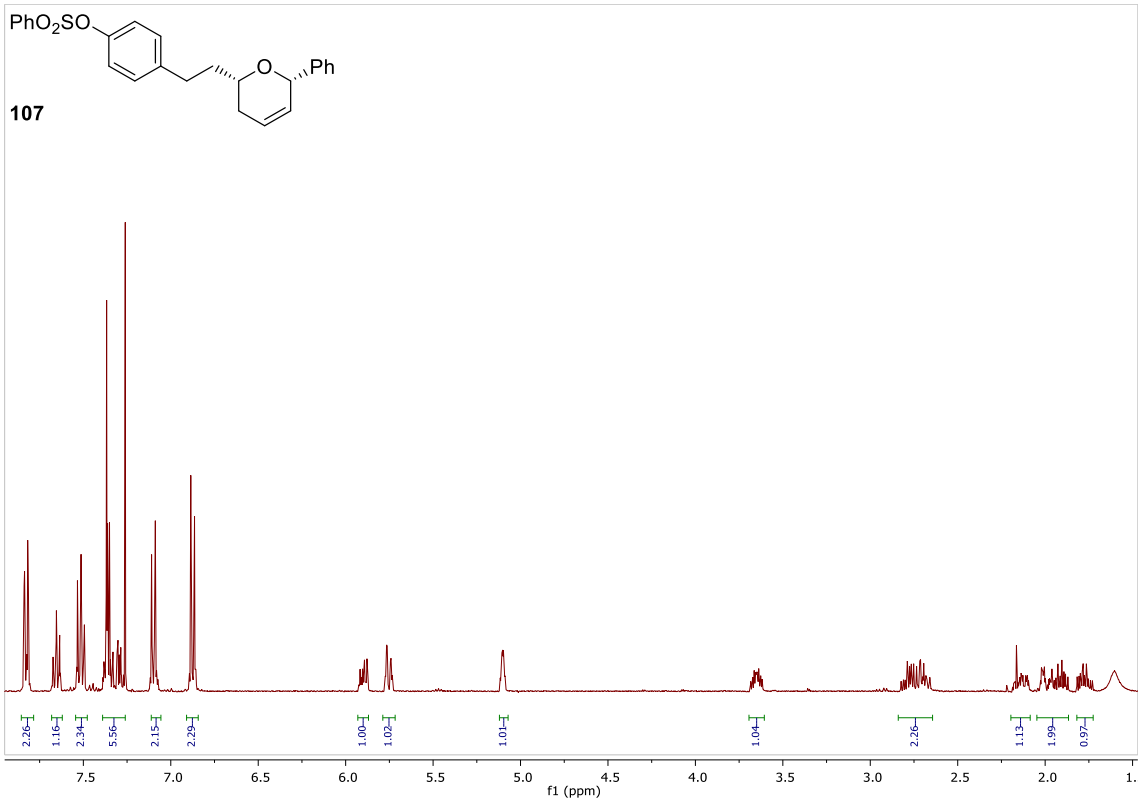

200.82
147.78
143.86
141.20
135.59
134.22
134.18
130.97
129.67
129.18
129.12
128.56
128.52
126.26
122.28
66.99
46.89
38.00
31.22
f1 (ppm)

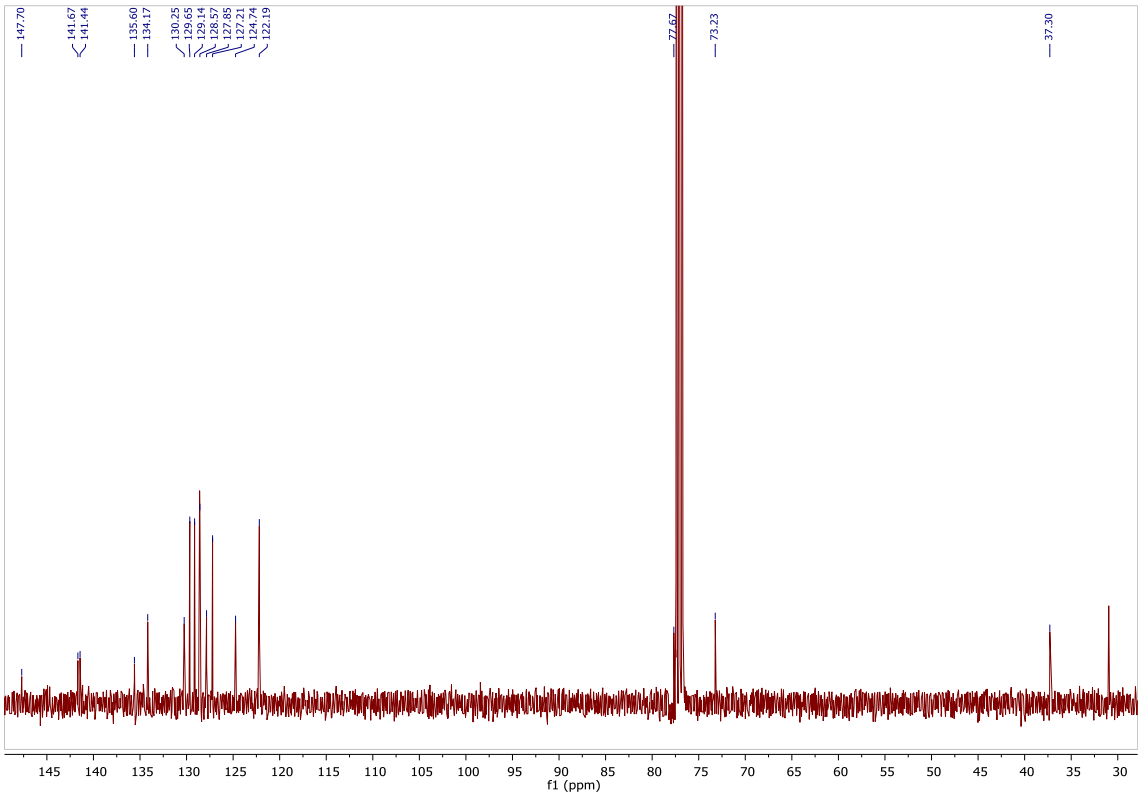

OH
OH
Ph
PhO2SO
104
2.65
1.32
2.65
7.45
2.60
2.62
1.06
1.07
0.99
1.15
2.84
4.50
f1 (ppm)

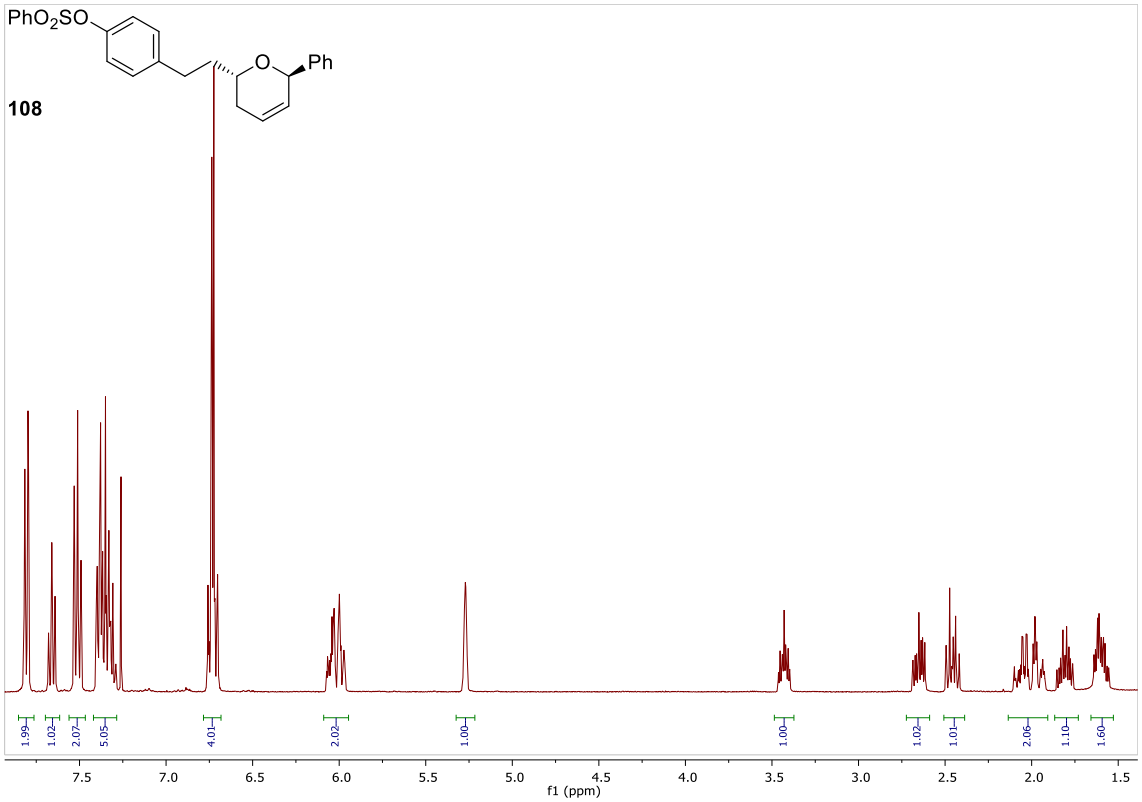

147.76
141.24
136.47
135.61
134.22
131.71
130.39
130.02
129.18
128.71
128.56
127.95
126.58
122.28
73.88
71.43
43.36
39.50
31.08
f1 (ppm)

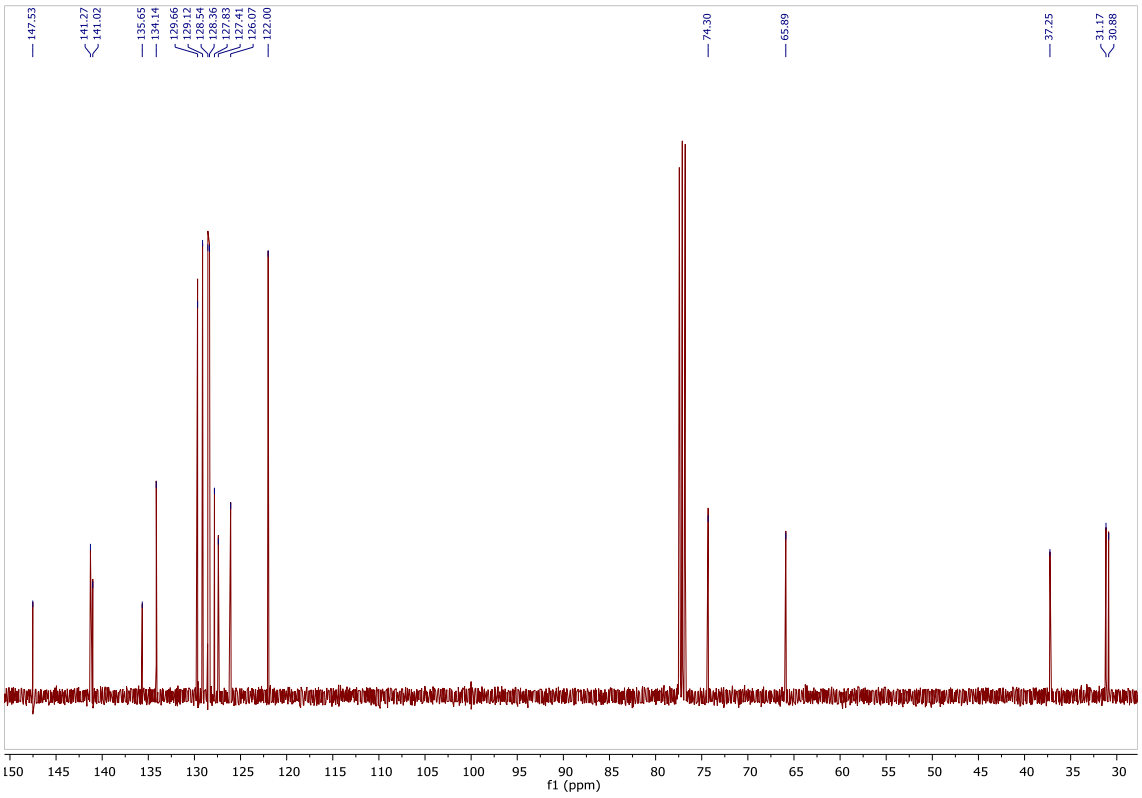

OH
OH
Ph
PhO2SO
106
2.61
1.32
2.65
6.39
2.43
2.66
1.08
1.04
1.00
1.01
4.52
5.63
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

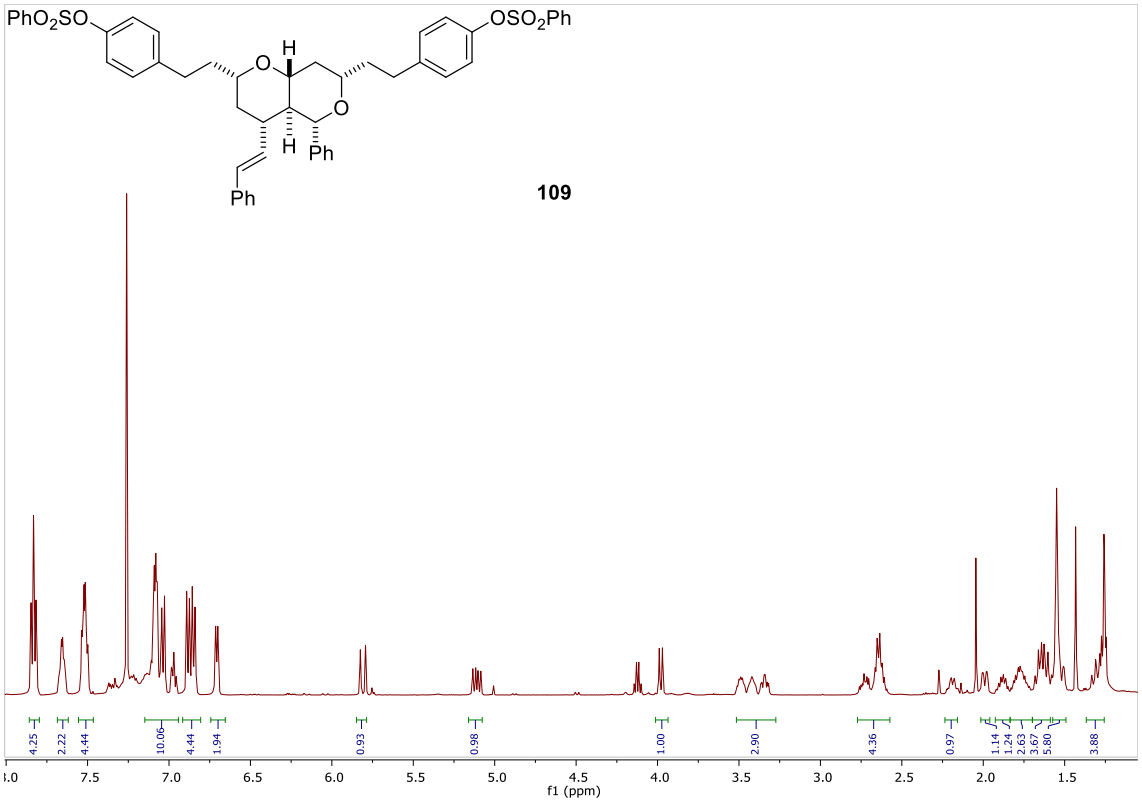

147.75
141.26
136.57
135.56
134.23
131.77
130.26
129.58
129.19
128.72
128.56
127.87
126.55
122.29
70.70
68.62
42.76
39.08
31.48
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
f1 (ppm)

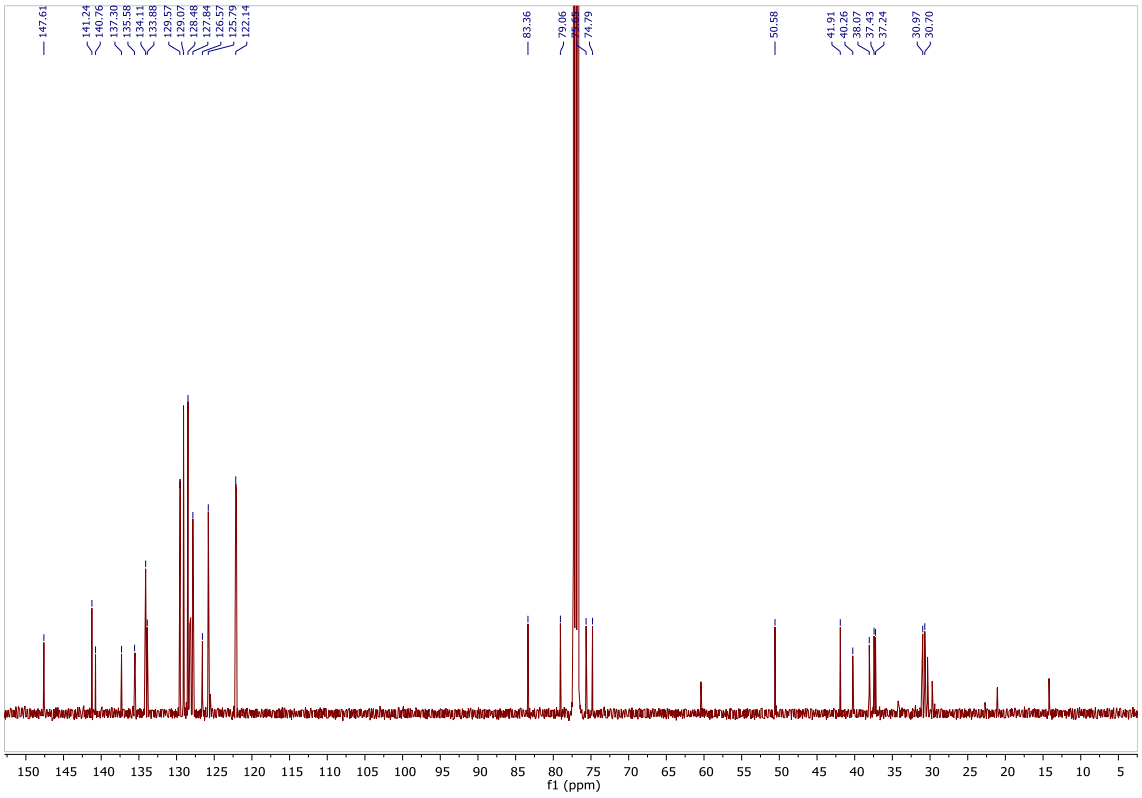

PhO2SO
O
Ph
107
2.26
1.16
2.34
5.56
2.15
2.29
1.00
1.02
1.01
1.04
2.26
1.13
1.99
0.97
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

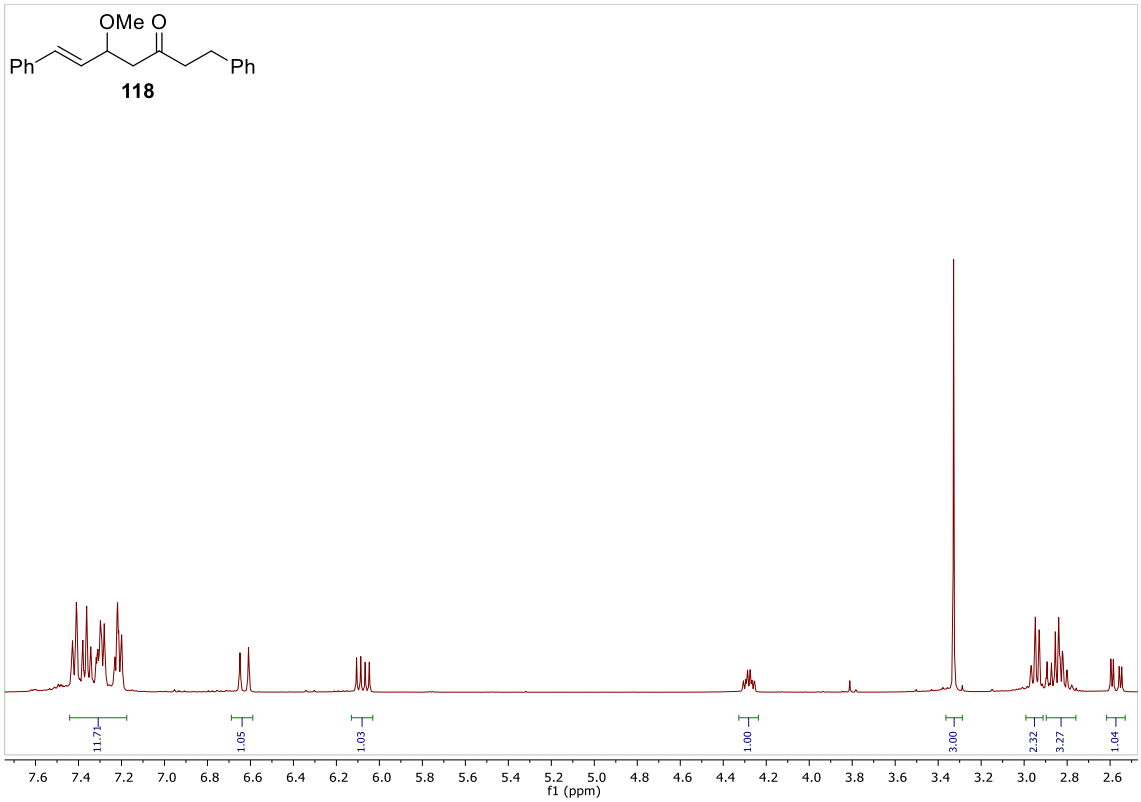

147.70
141.67
141.44
135.60
134.17
130.25
129.65
129.14
128.57
127.85
127.21
124.74
122.19
77.67
73.23
37.30
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
f1 (ppm)

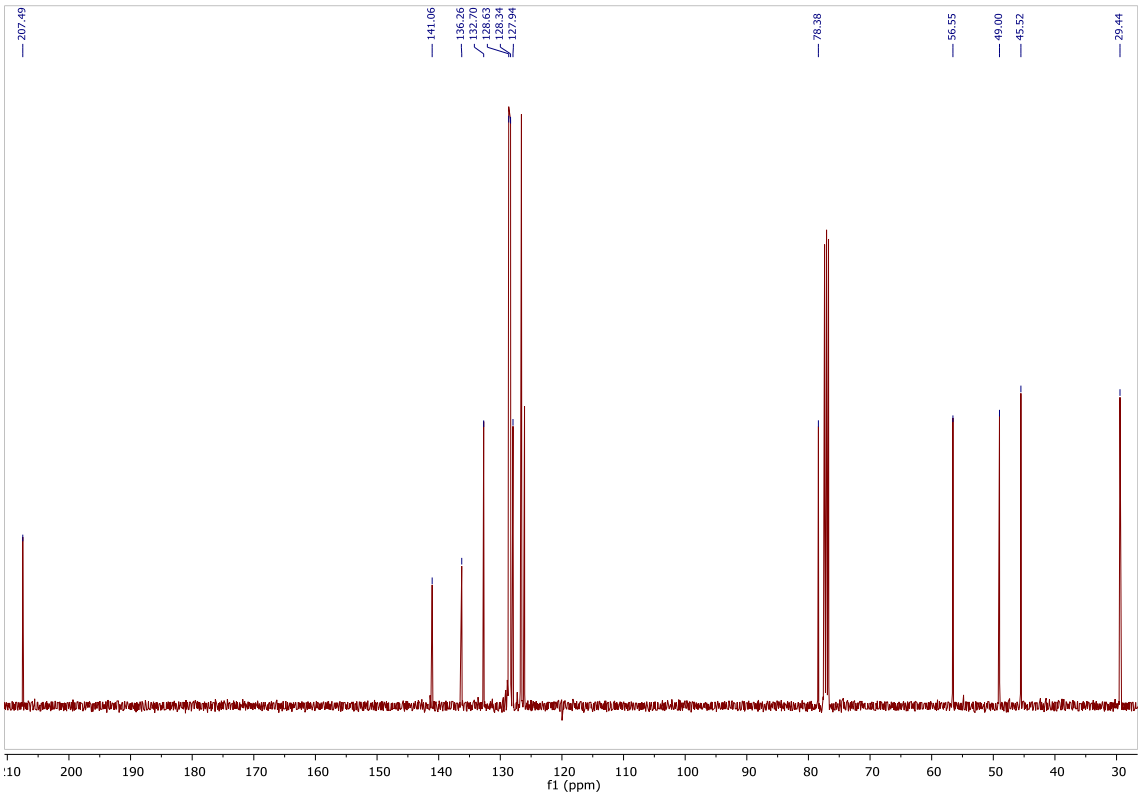

PhO2SO
O
Ph
108
1.99
1.02
2.07
5.05
4.01
2.02
1.00
1.00
1.02
1.01
2.06
1.10
1.60
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

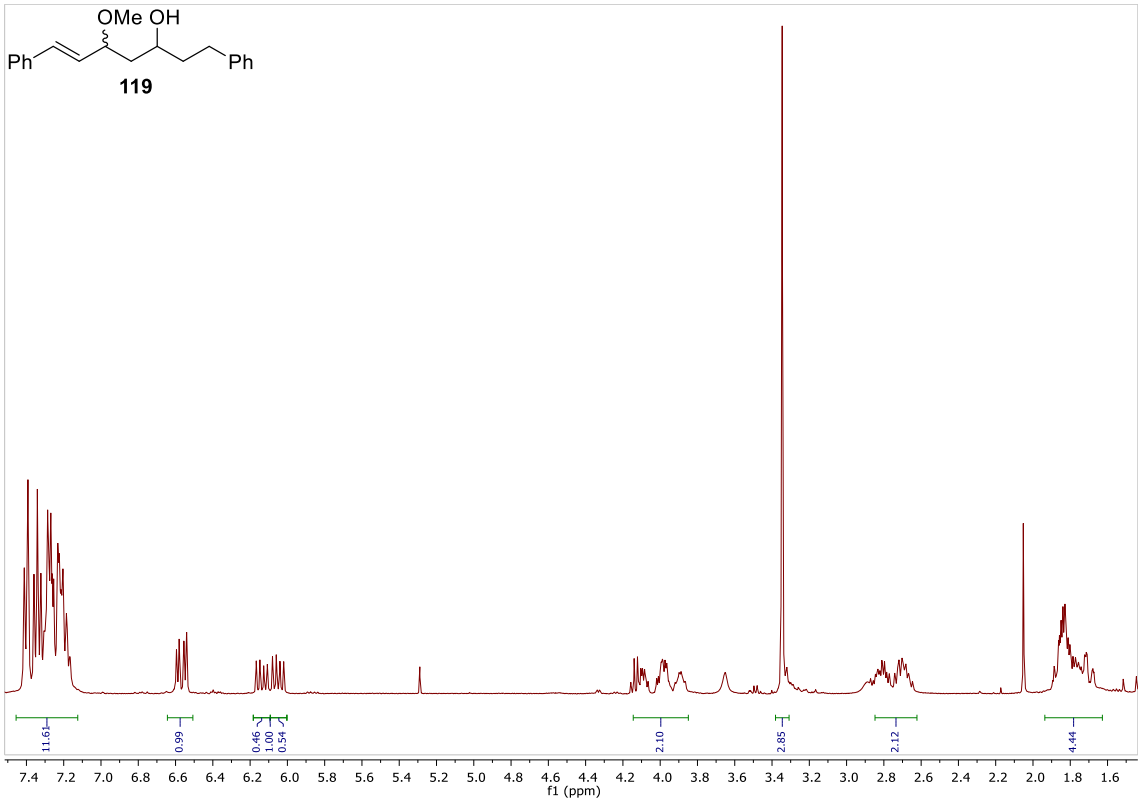

147.53
141.27
141.02
135.65
134.14
129.66
129.12
128.54
128.36
127.83
127.41
126.07
122.00
74.30
65.89
37.25
31.17
30.88
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
f1 (ppm)

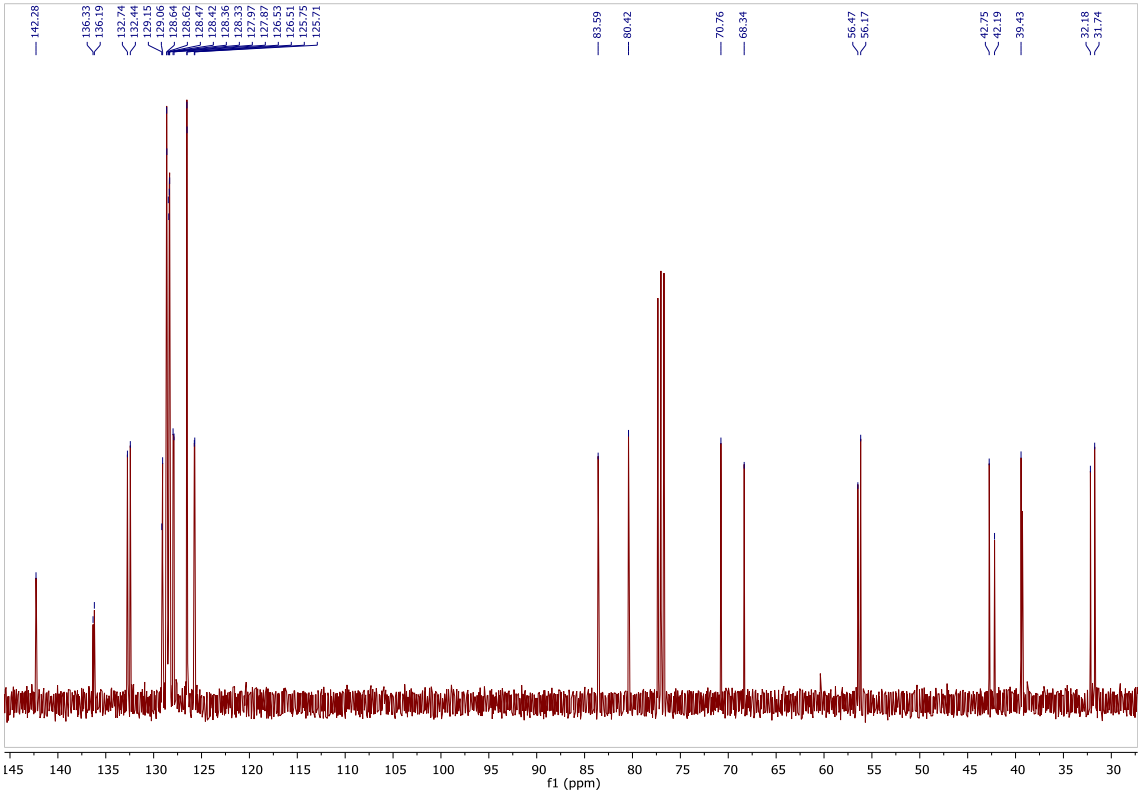

PhO2SO
OSO2Ph
H
O
O
H
Ph
Ph
109
4.25
2.22
4.44
10.06
4.44
1.94
0.93
0.98
1.00
2.90
4.36
0.97
1.14
1.24
2.63
3.67
5.80
3.88
f1 (ppm)

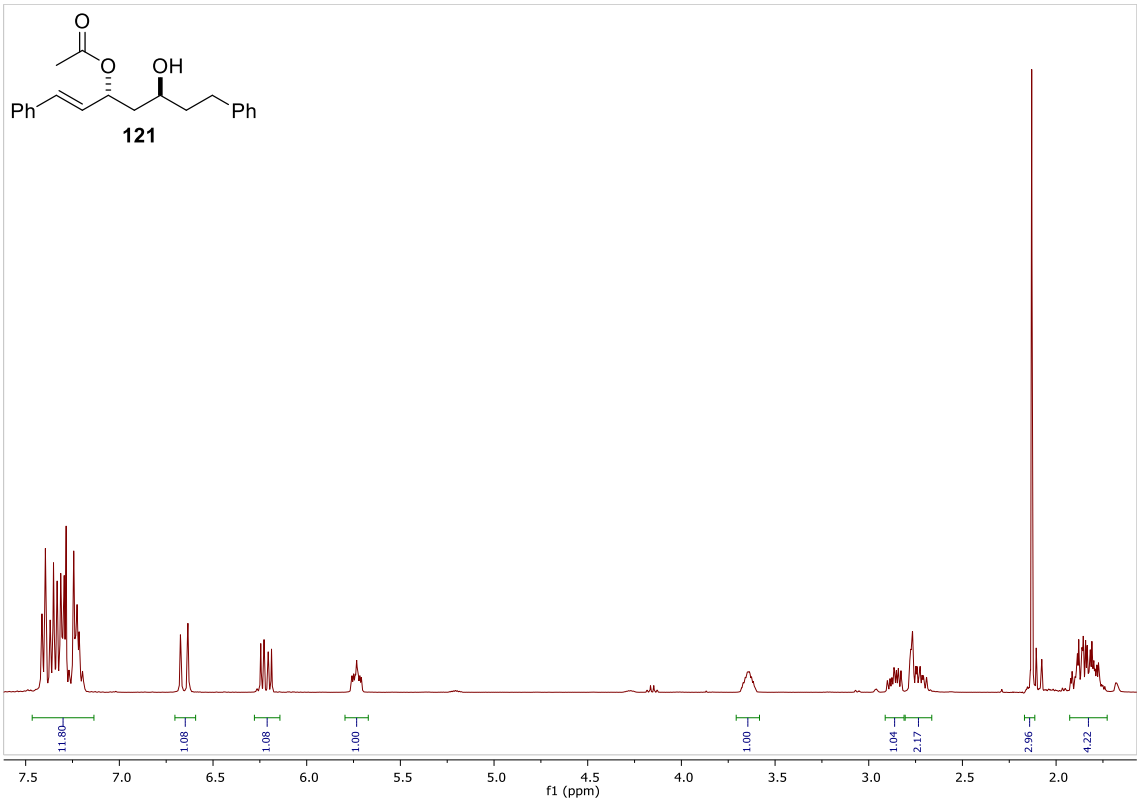

147.61
141.24
140.76
137.30
135.58
134.11
133.88
129.57
129.07
128.48
127.84
126.57
125.79
122.14
83.36
79.06
78.66
74.79
50.58
41.91
40.26
38.07
37.43
37.24
30.97
30.70
f1 (ppm)

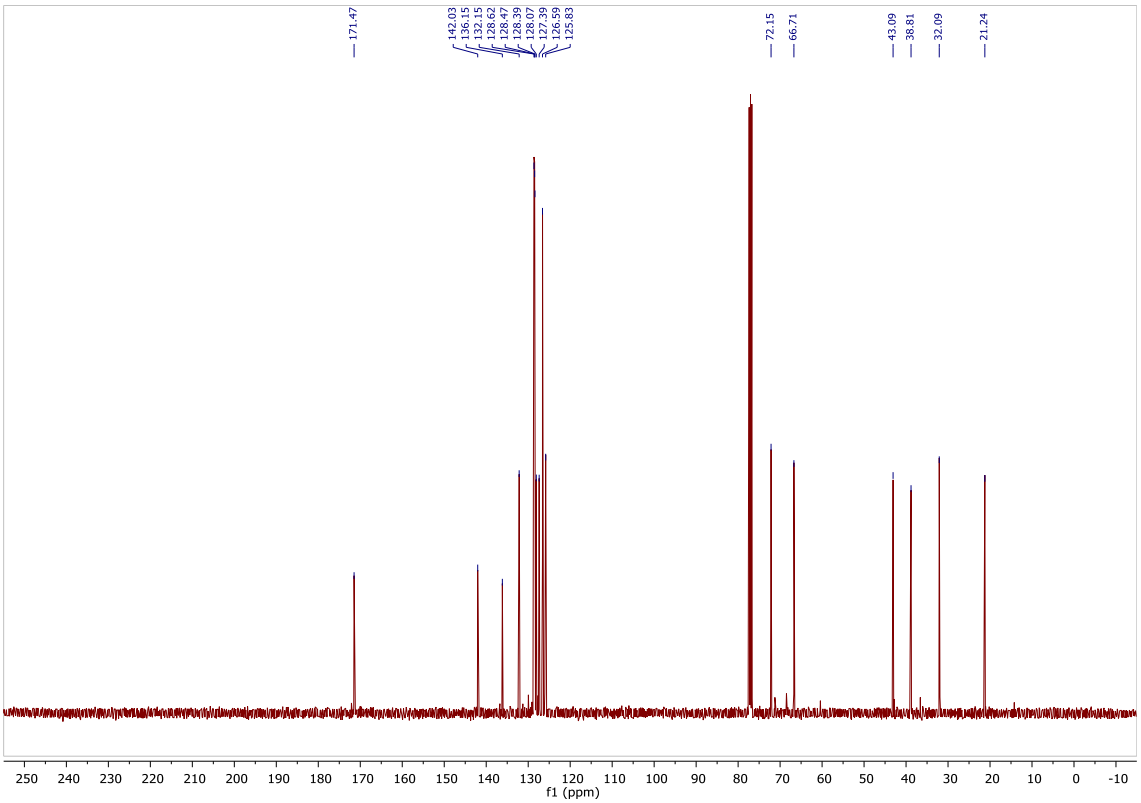

OMe O
Ph
Ph
118
11.71
1.05
1.03
1.00
3.00
2.32
3.27
1.04
f1 (ppm)

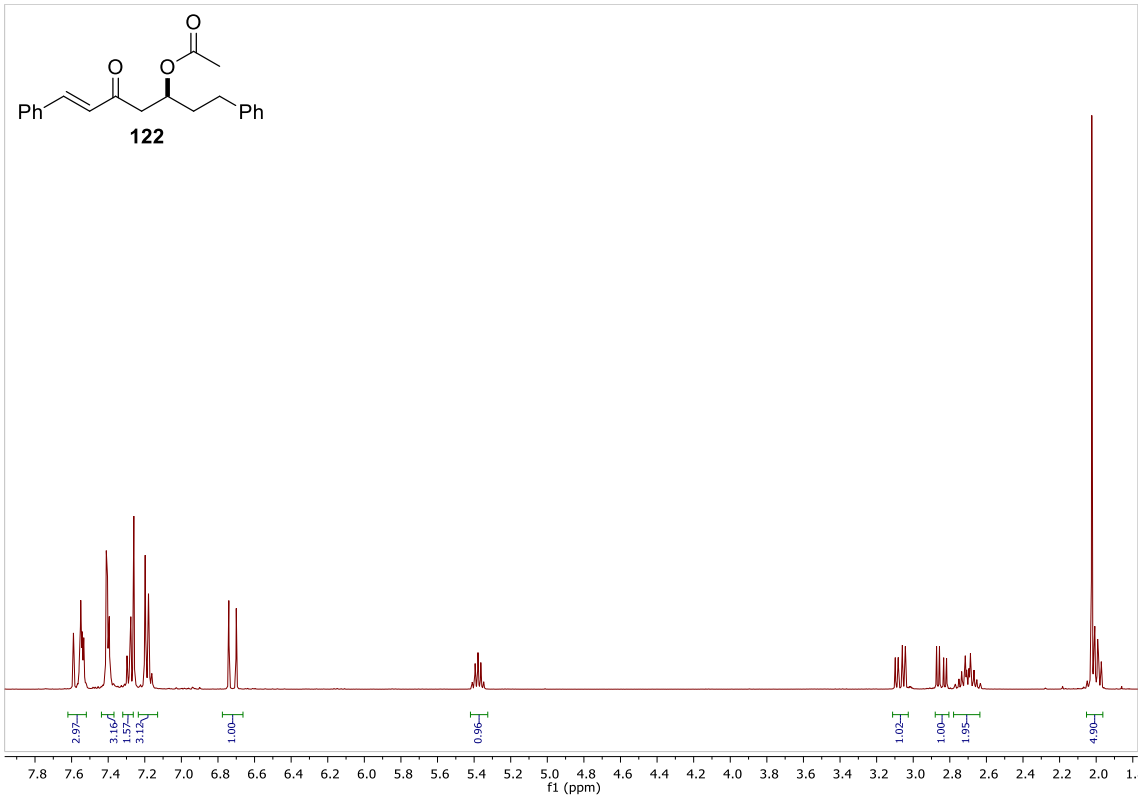

207.49
141.06
136.26
132.70
128.63
128.34
127.94
78.38
56.55
49.00
45.52
29.44
f1 (ppm)

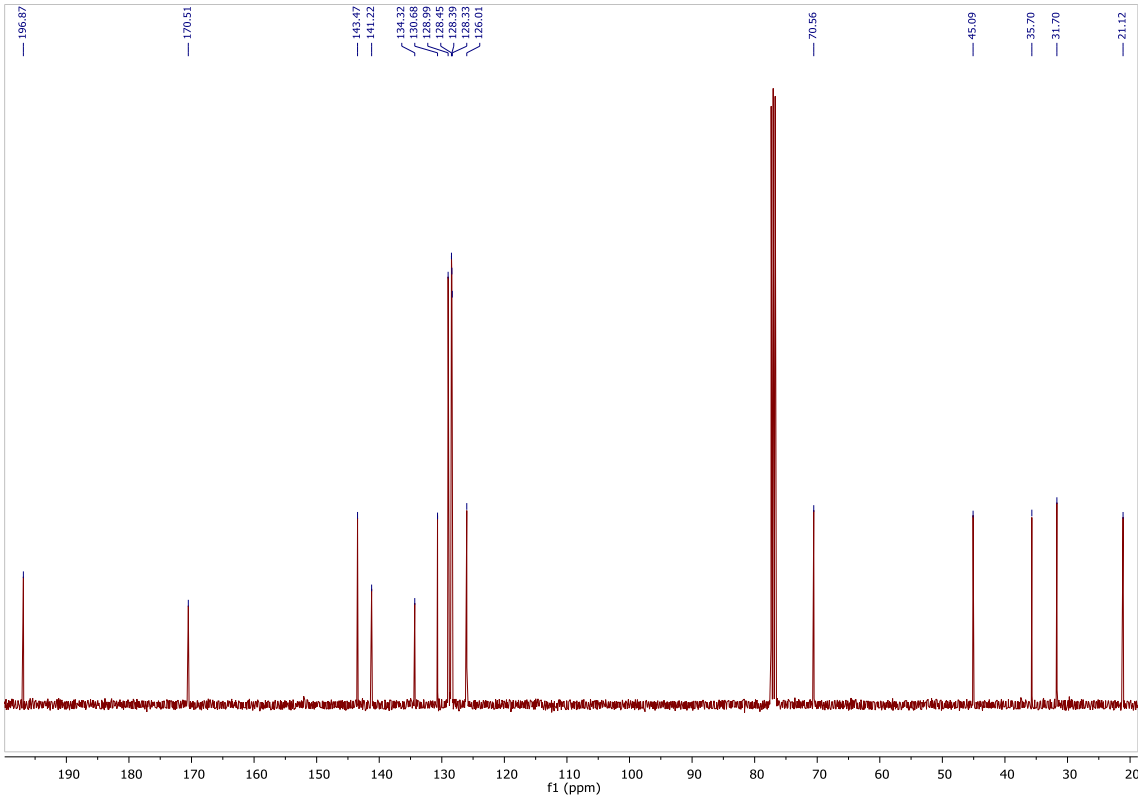

OMe OH
Ph
Ph
119
11.61
0.99
0.46
1.00
0.54
2.10
2.85
2.12
4.44
f1 (ppm)

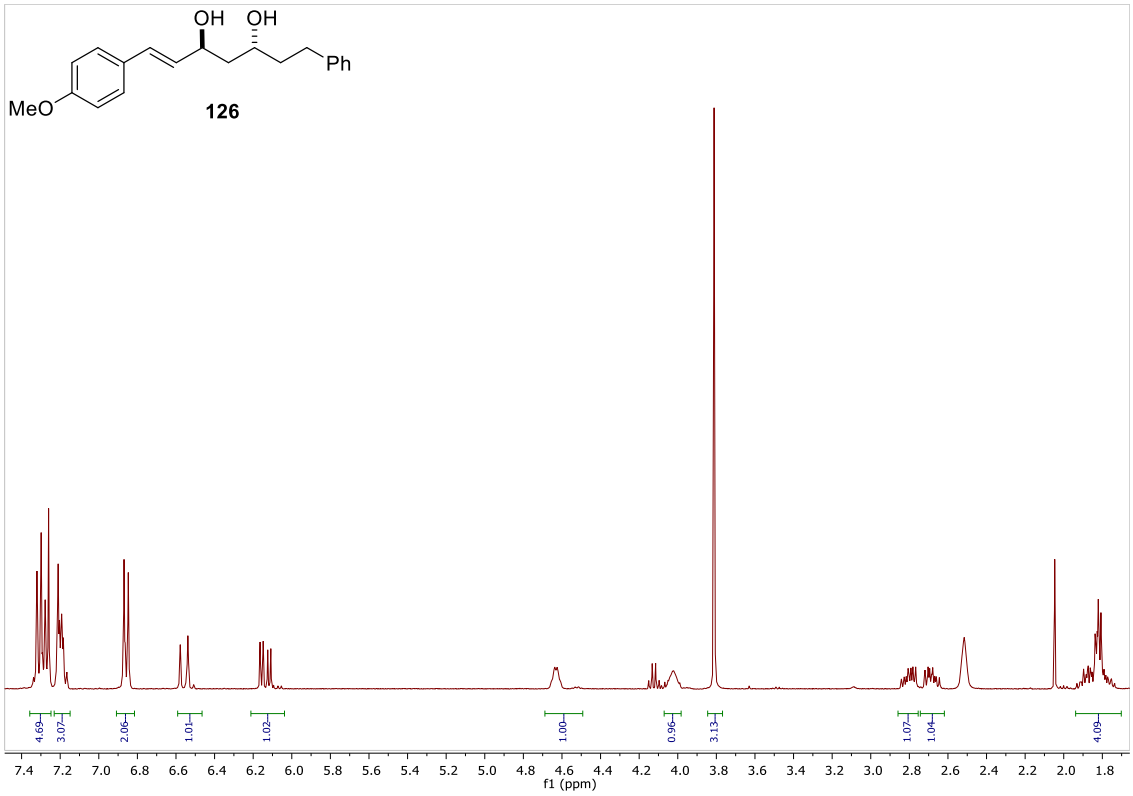

142.28
136.33
136.19
132.74
132.44
129.15
129.06
128.64
128.62
128.47
128.42
128.36
128.33
127.97
127.87
126.53
126.51
125.75
125.71
83.59
80.42
70.76
68.34
56.47
56.17
42.75
42.19
39.43
32.18
31.74
f1 (ppm)

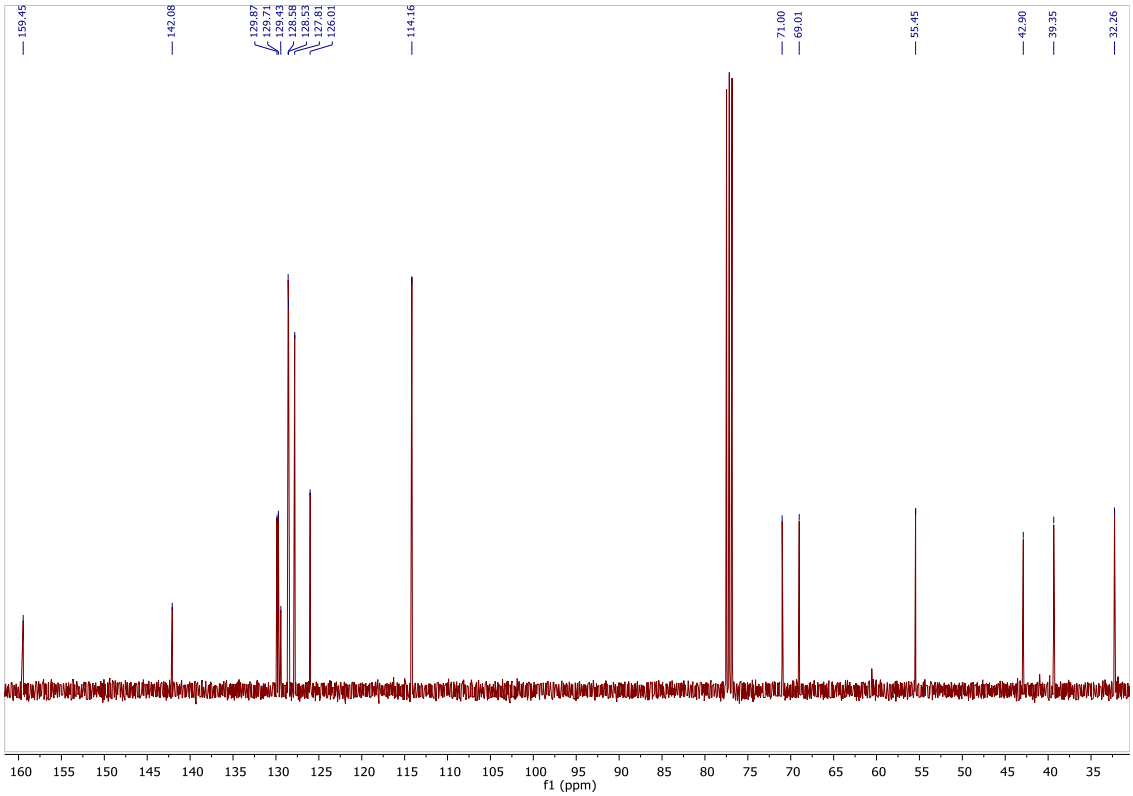

O
O
OH
Ph
Ph
121
11.80
1.08
1.08
1.00
1.00
1.04
2.17
2.96
4.22
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

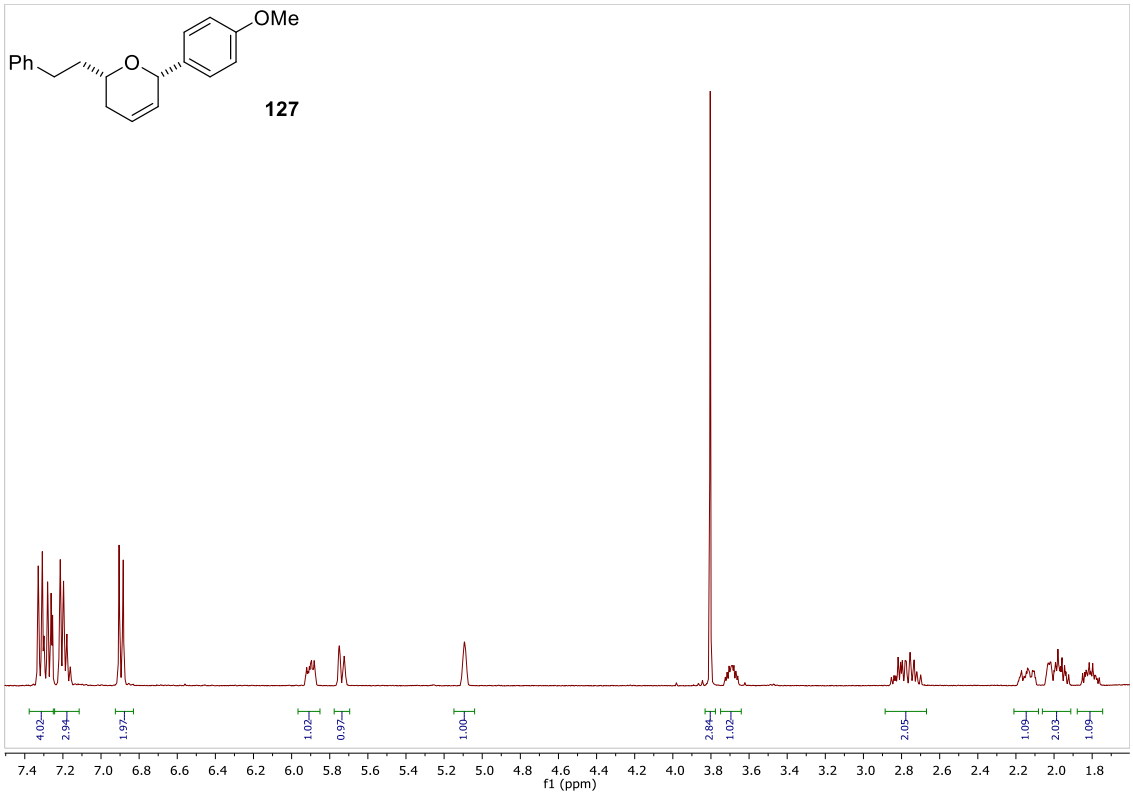

171.47
142.03
136.15
132.15
128.62
128.47
128.39
128.07
127.39
126.59
125.83
72.15
66.71
43.09
38.81
32.09
21.24
250
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

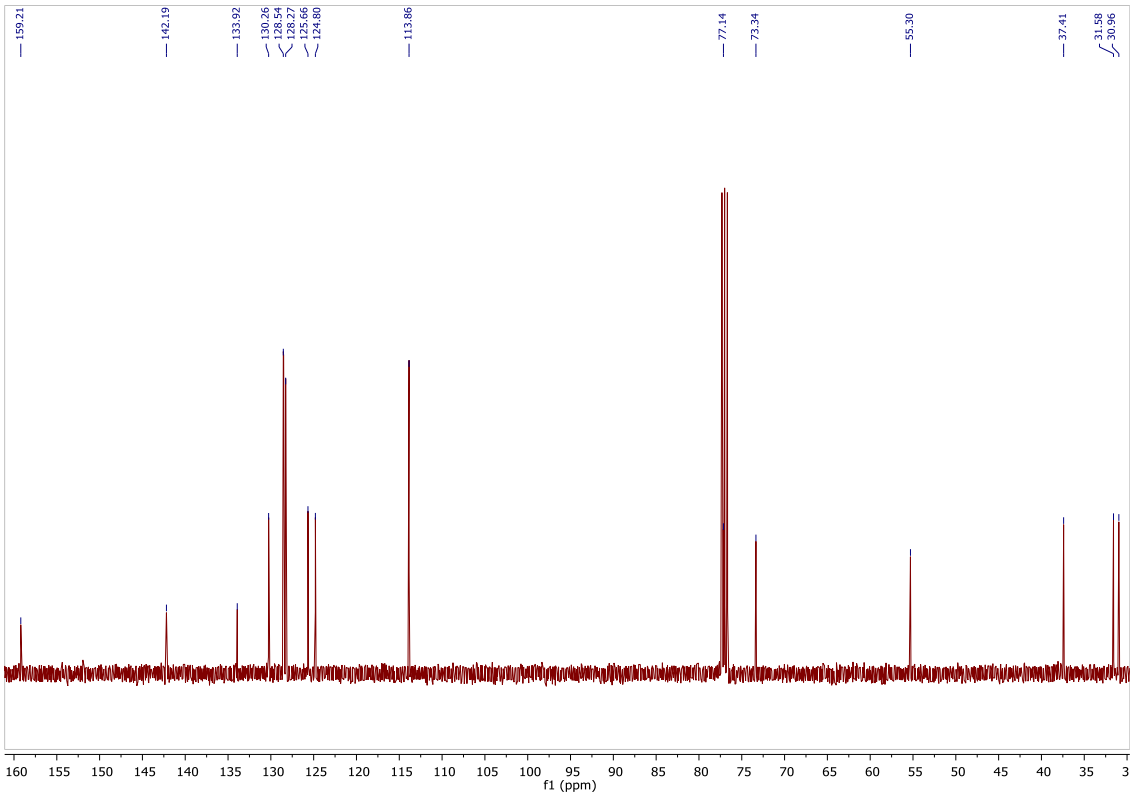

O
O
O
Ph
Ph
122
2.97
3.16
1.57
3.12
1.00
0.96
1.02
1.00
1.95
4.90
f1 (ppm)

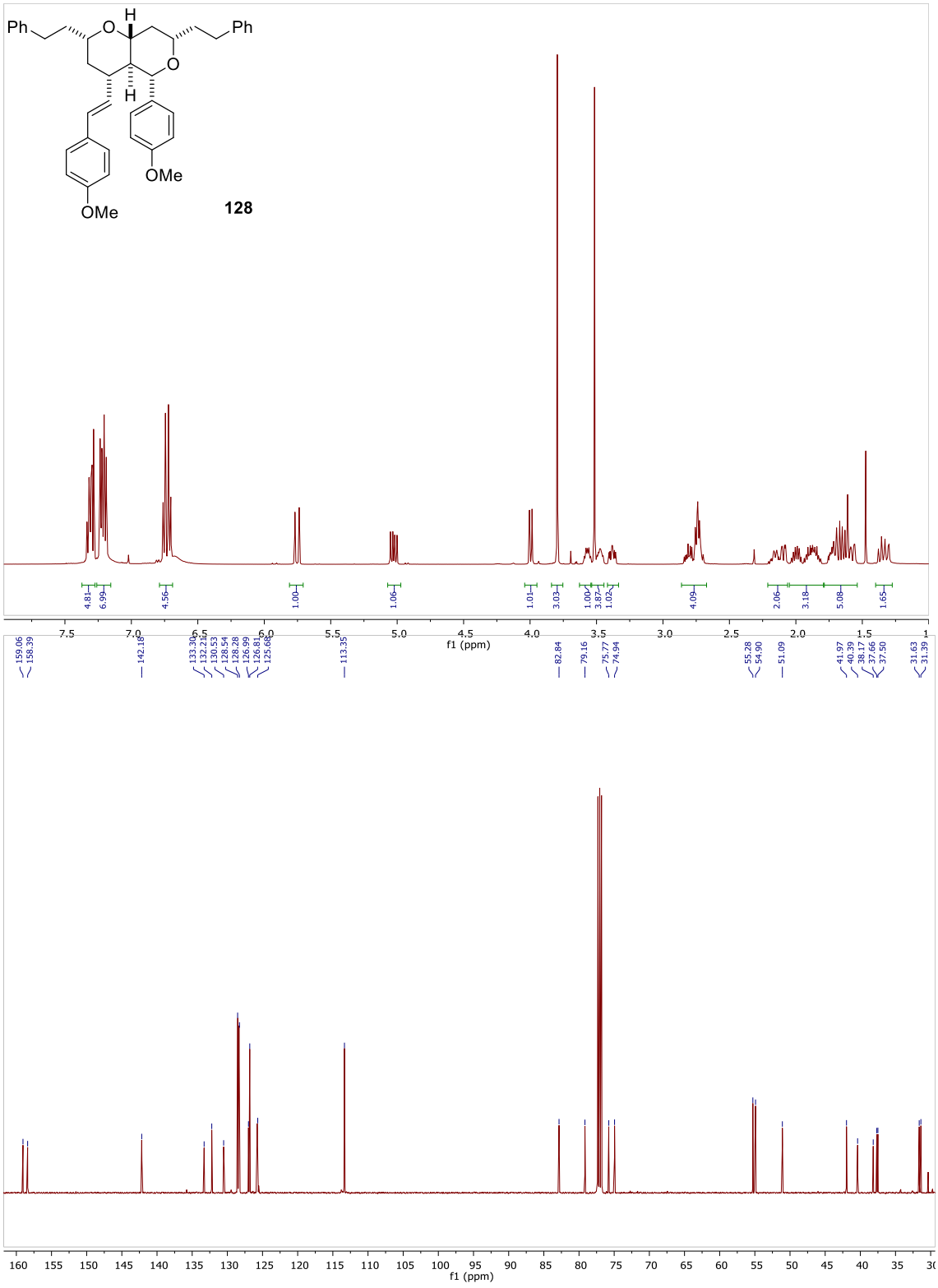

196.87
170.51
143.47
141.22
134.32
130.68
128.99
128.45
128.39
128.33
126.01
70.56
45.09
35.70
31.70
21.12
f1 (ppm)

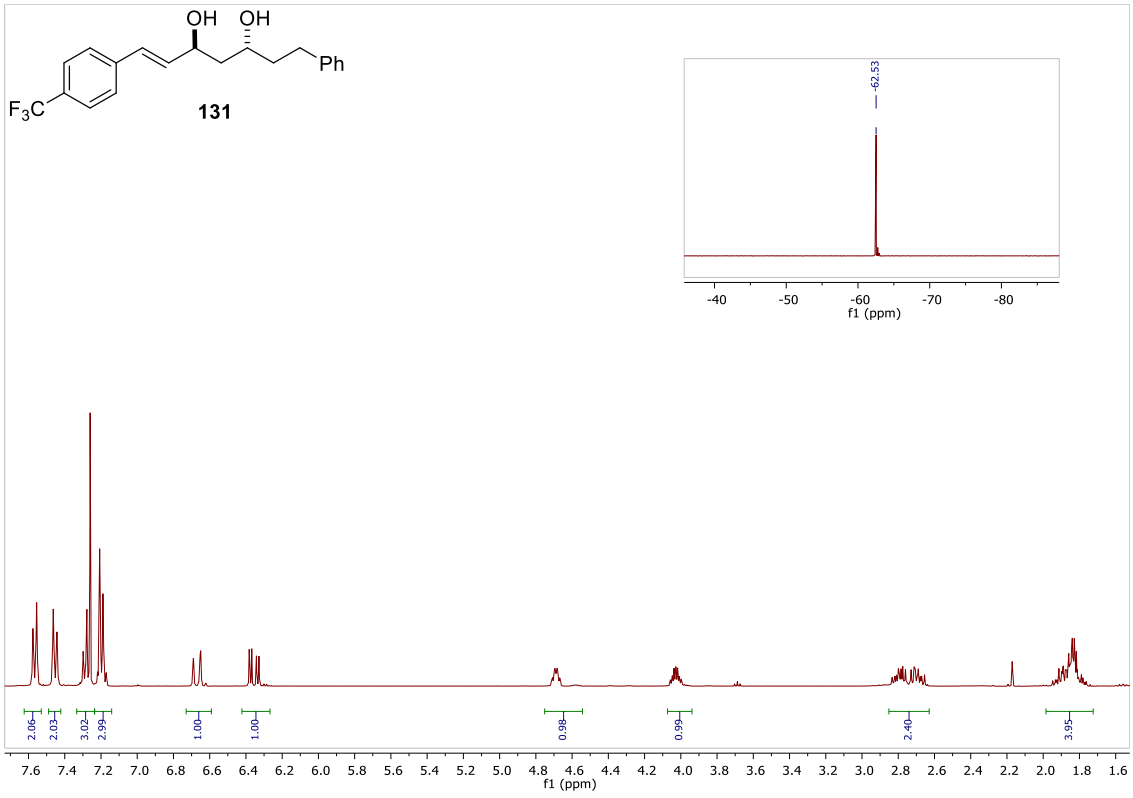

OH
OH
Ph
MeO
126
4.69
3.07
2.06
1.01
1.02
1.00
0.96
3.13
1.07
1.04
4.09
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8
f1 (ppm)

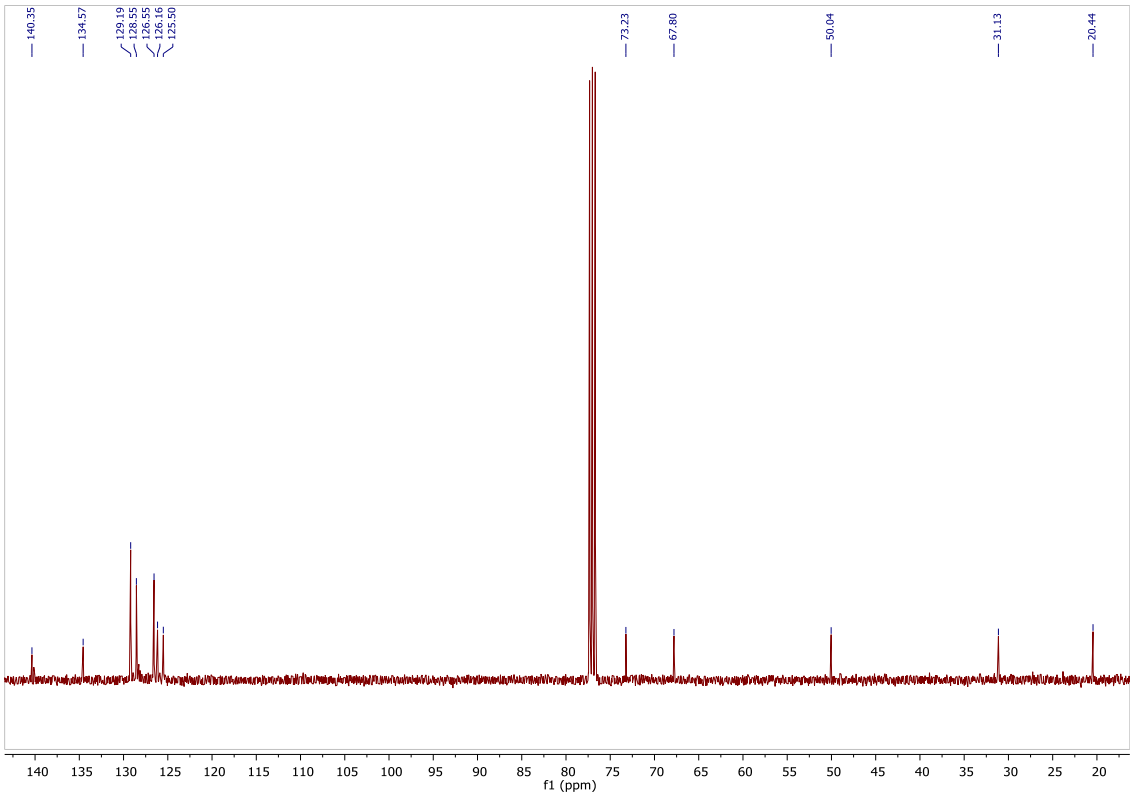

159.45
142.08
129.87
129.71
129.43
128.58
128.53
127.81
126.01
114.16
71.00
69.01
55.45
42.90
39.35
32.26
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35
f1 (ppm)

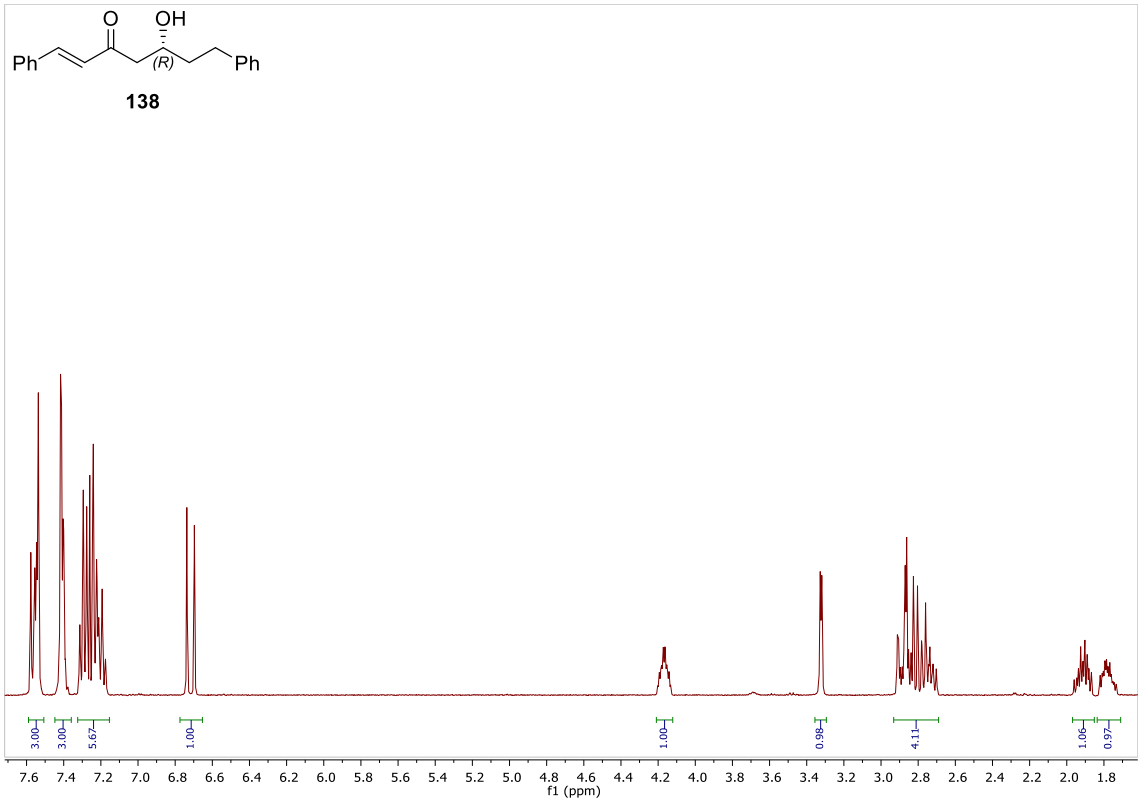

OMe
Ph
O
127
4.02
2.94
1.97
1.02
0.97
1.00
2.84
1.02
2.05
1.09
2.03
1.09
f1 (ppm)

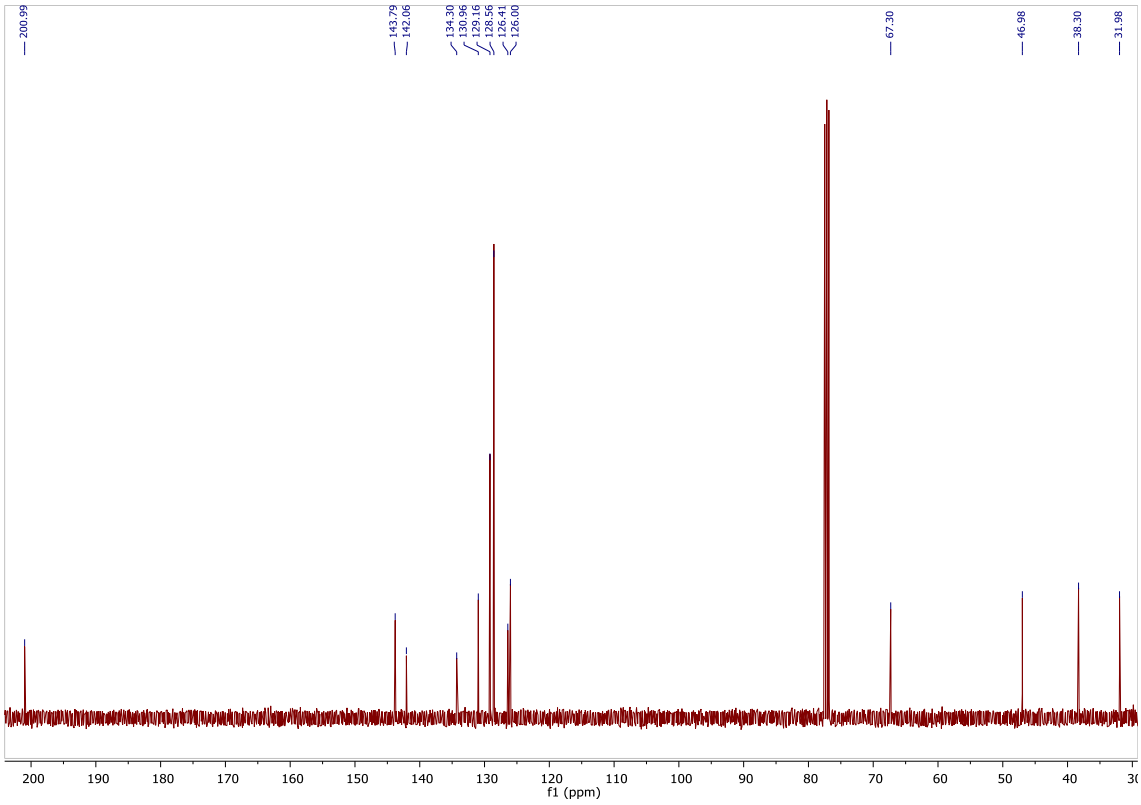

159.21
142.19
133.92
130.26
128.54
128.27
125.66
124.80
113.86
77.14
73.34
55.30
37.41
31.58
30.96
f1 (ppm)

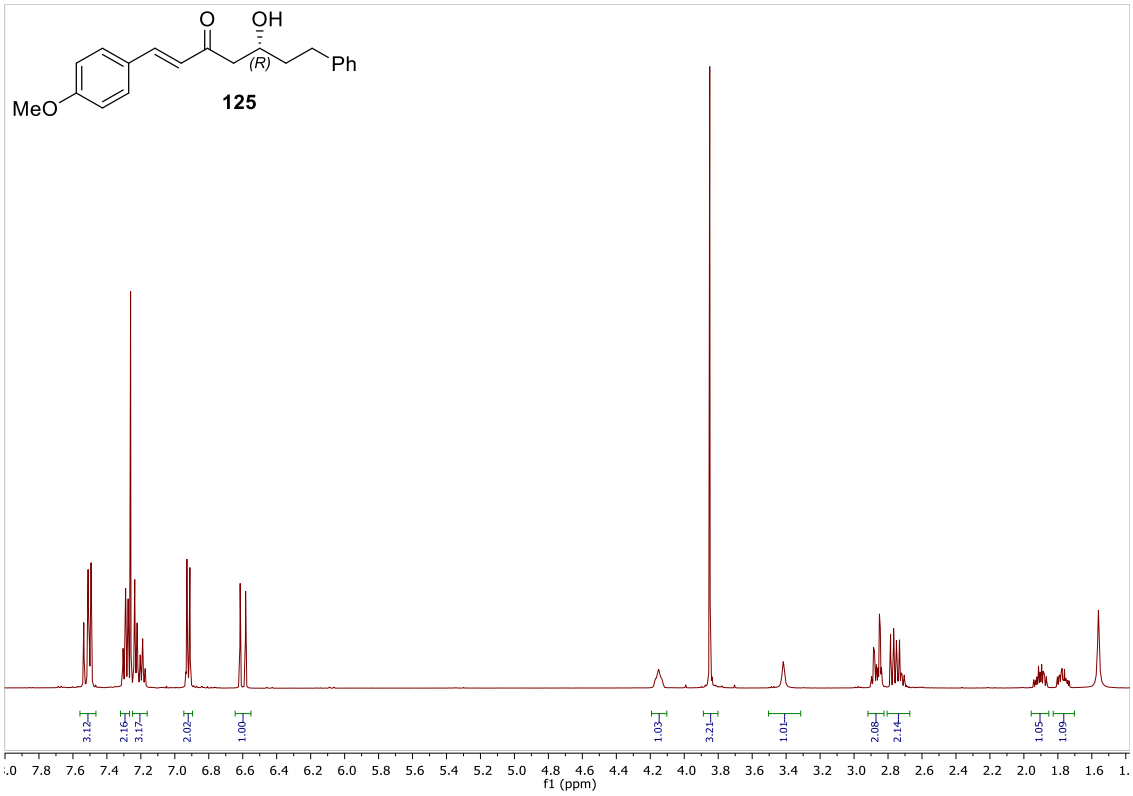

Ph
O
H
Ph
O
H
OMe
OMe
128
4.81
6.99
4.56
1.00
1.06
1.01
3.03
1.00
3.87
1.02
4.09
2.06
3.18
5.08
1.65
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1
f1 (ppm)
159.06
158.39
142.18
133.30
132.25
130.53
128.54
128.28
126.99
126.81
125.66
113.35
82.84
79.16
75.77
74.94
55.28
54.90
51.09
41.97
40.39
38.17
37.66
37.50
31.63
31.39
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
f1 (ppm)

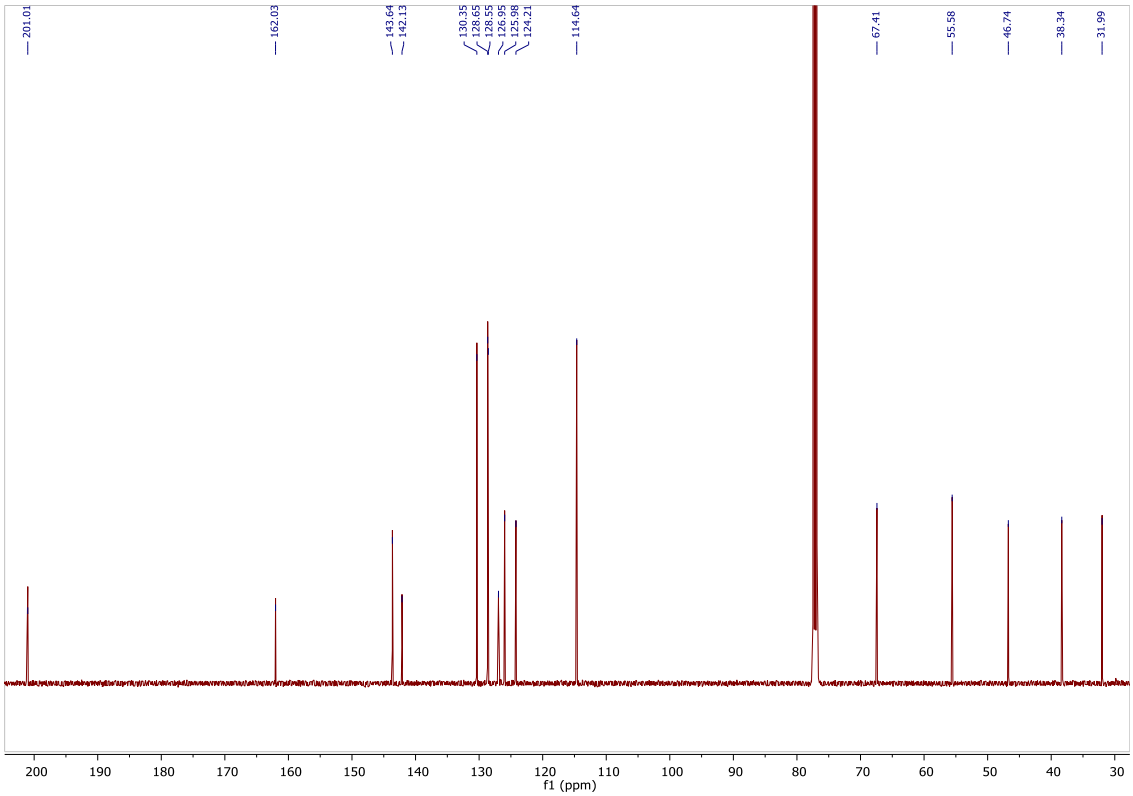

OH
OH
Ph
F3C
131
-62.53
-40
-50
-60
-70
-80
f1 (ppm)
2.06
2.03
3.02
2.99
1.00
1.00
0.98
0.99
2.40
3.95
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)

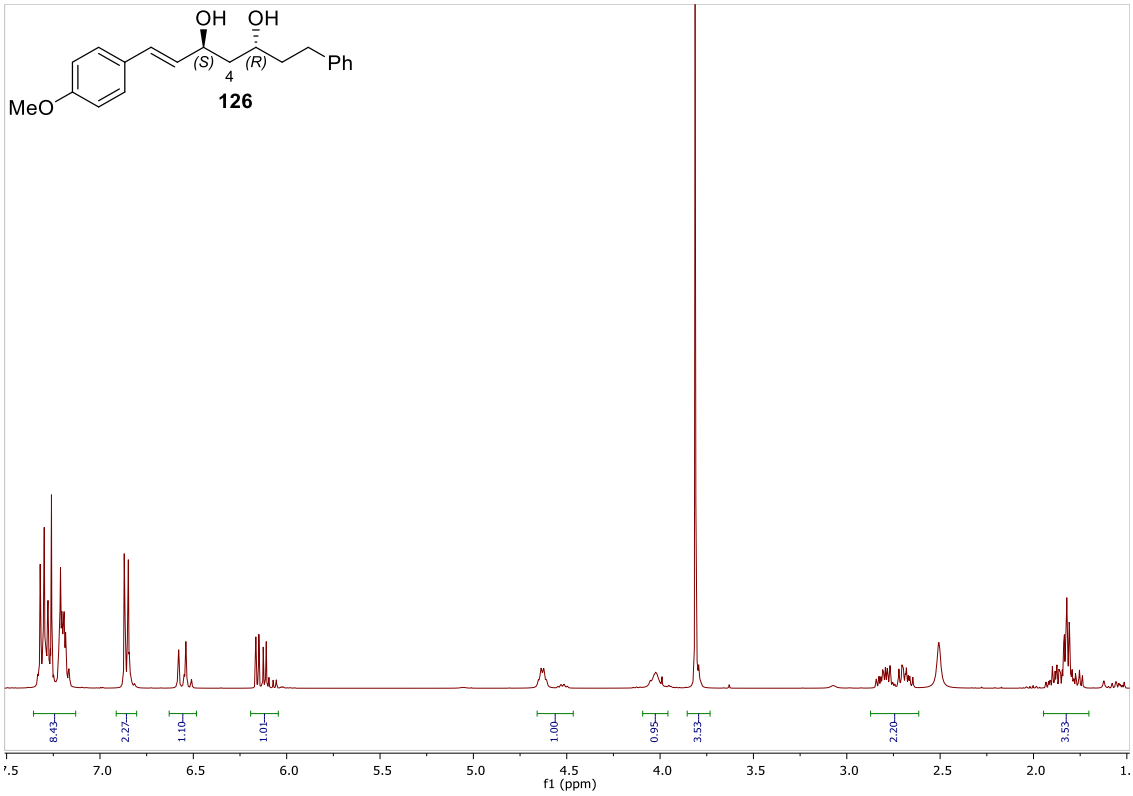

140.35
134.57
129.19
128.55
126.55
126.16
125.50
73.23
67.80
50.04
31.13
20.44
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)

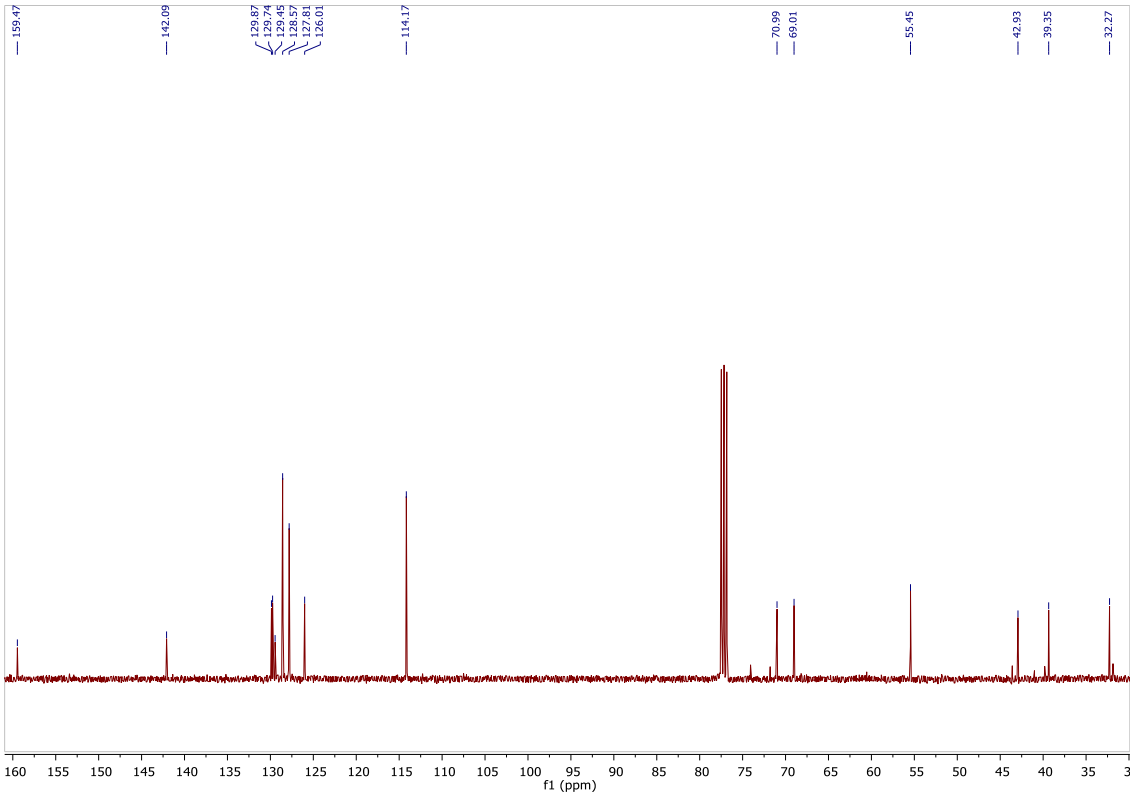

O
OH
Ph
(R)
Ph
138
3.00
3.00
5.67
1.00
1.00
0.98
4.11
1.06
0.97
f1 (ppm)

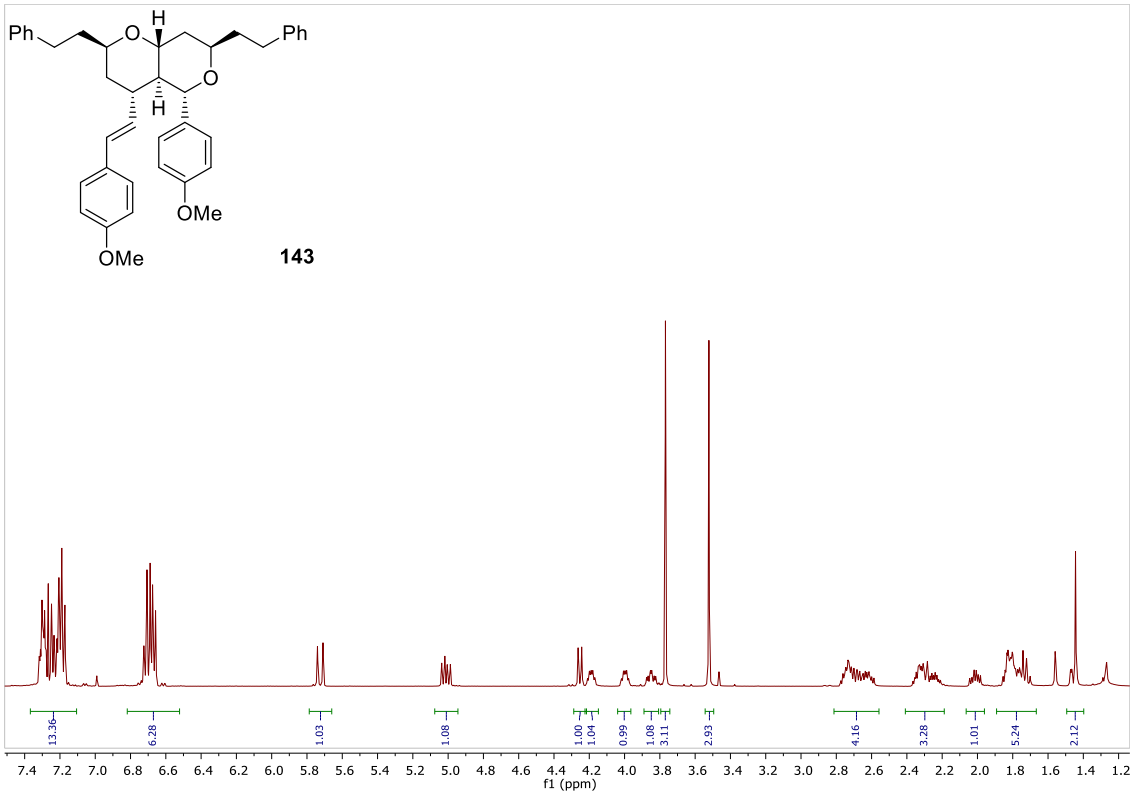

200.99
143.79
142.06
134.30
130.96
129.16
128.56
126.41
126.00
67.30
46.98
38.30
31.98
f1 (ppm)

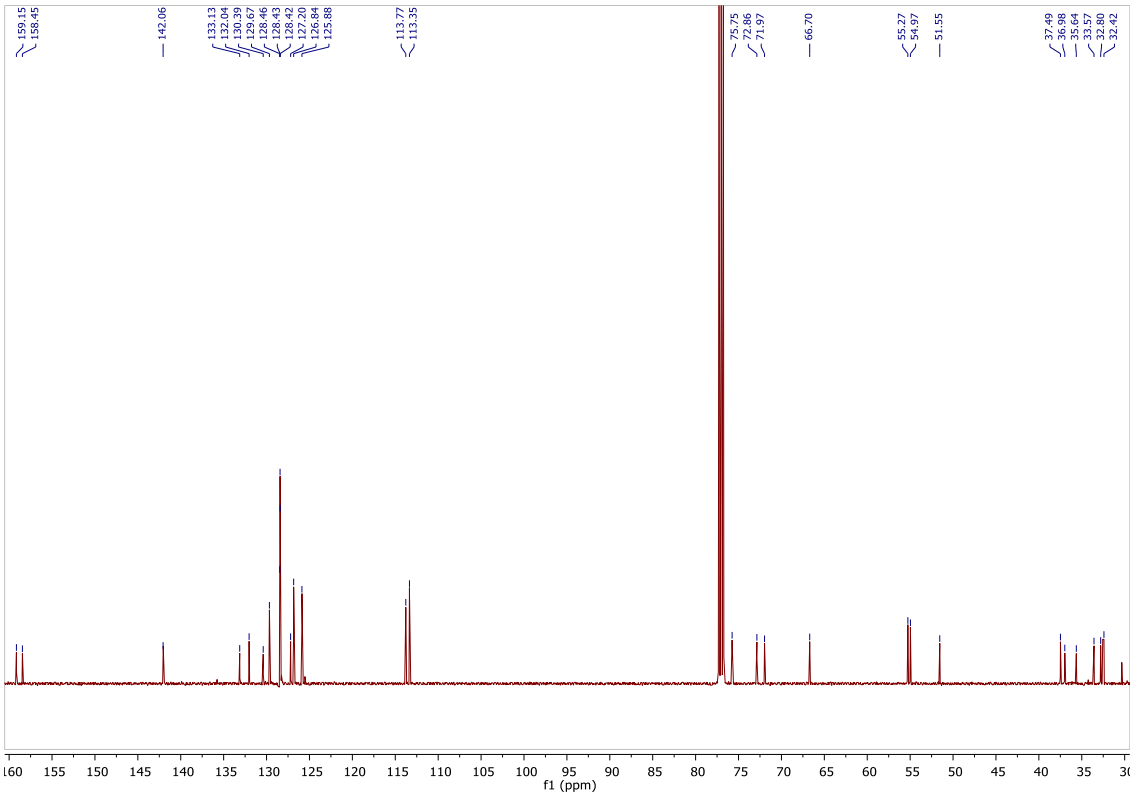

O
OH
(R)
Ph
MeO
125
3.12
2.16
3.17
2.02
1.00
1.03
3.21
1.01
2.08
2.14
1.05
1.09
f1 (ppm)

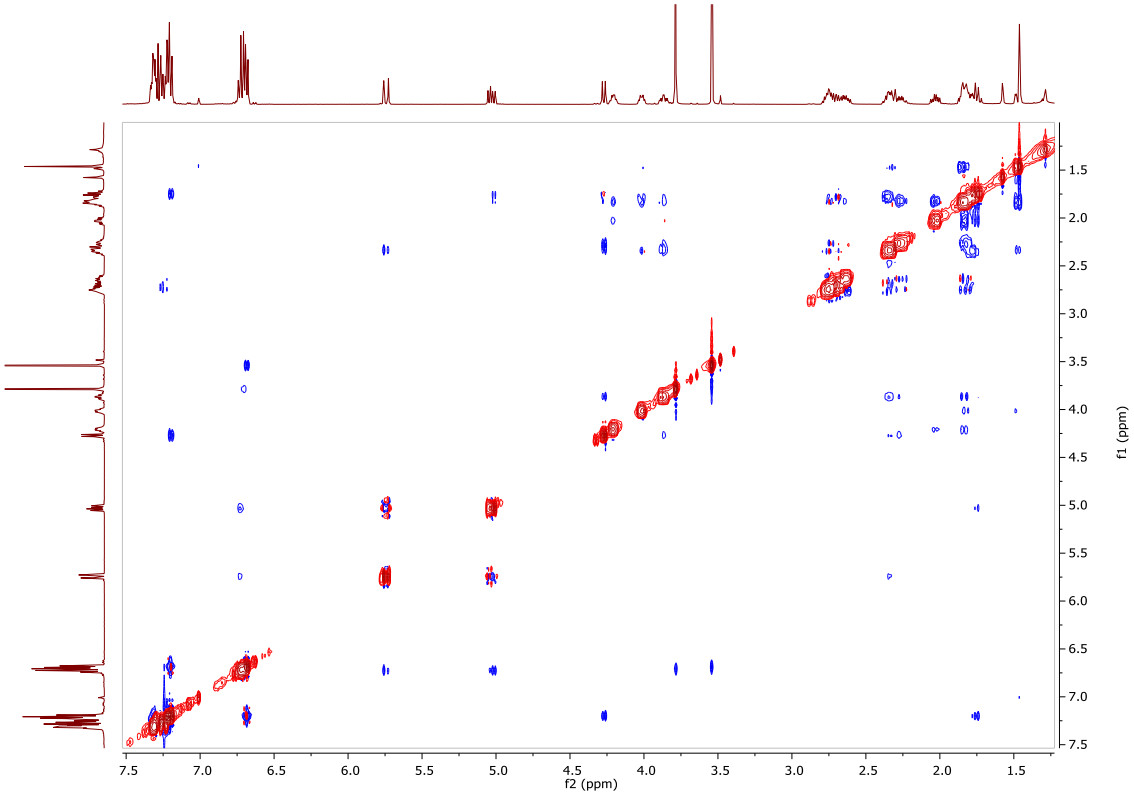

201.01
162.03
143.64
142.13
130.35
128.65
128.55
126.95
125.98
124.21
114.64
67.41
55.58
46.74
38.34
31.99
f1 (ppm)

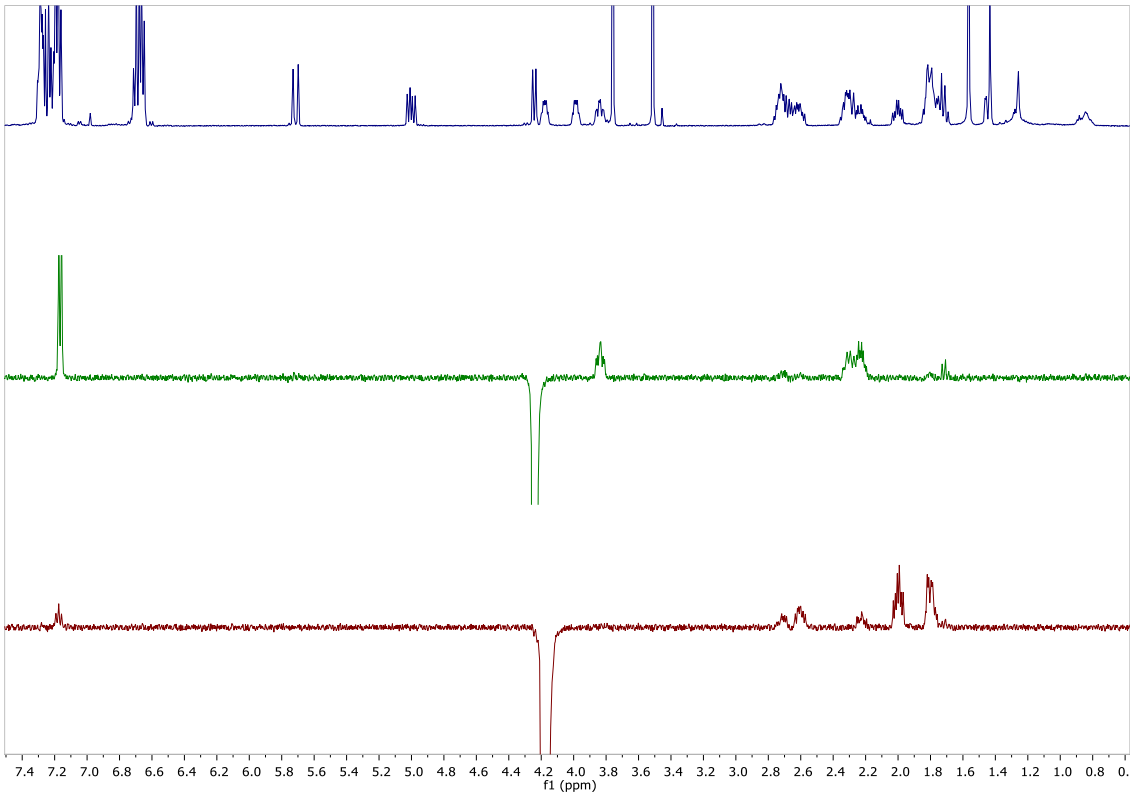

OH
OH
(S)
(R)
4
Ph
MeO
126
8.43
2.27
1.10
1.01
1.00
0.95
3.53
2.20
3.53
f1 (ppm)

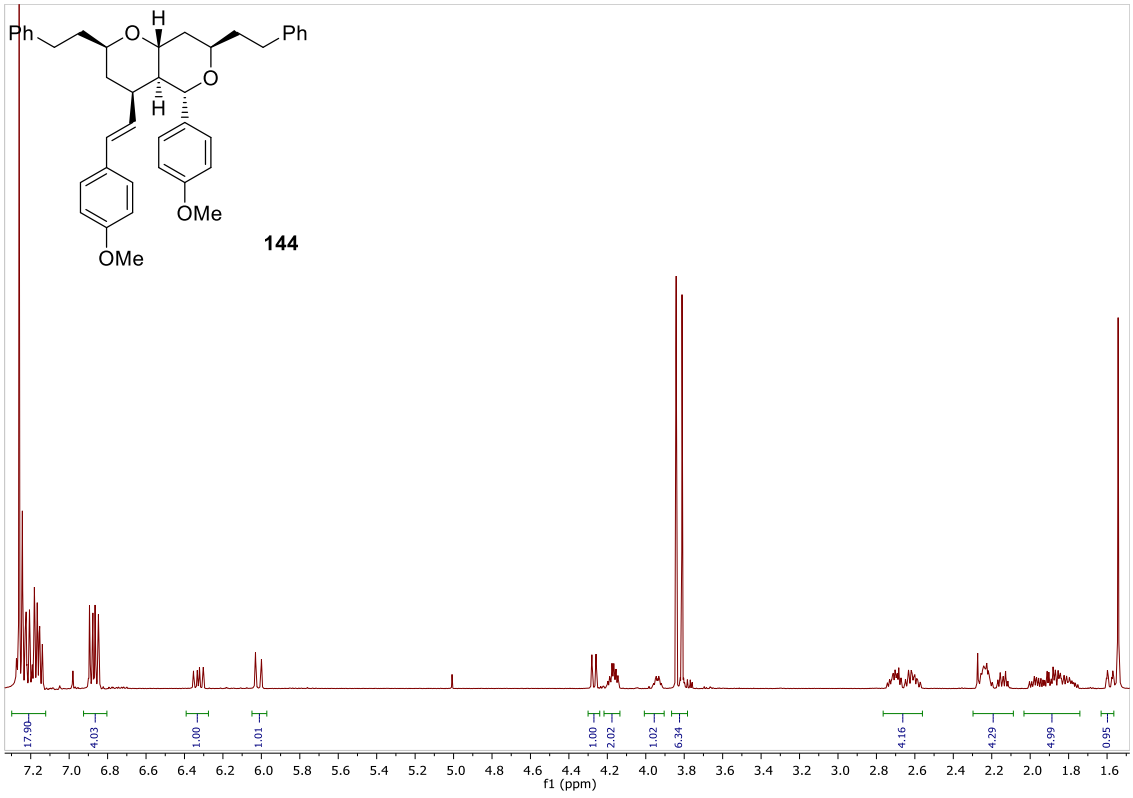

159.47
142.09
129.87
129.74
129.45
128.57
127.81
126.01
114.17
70.99
69.01
55.45
42.93
39.35
32.27
f1 (ppm)

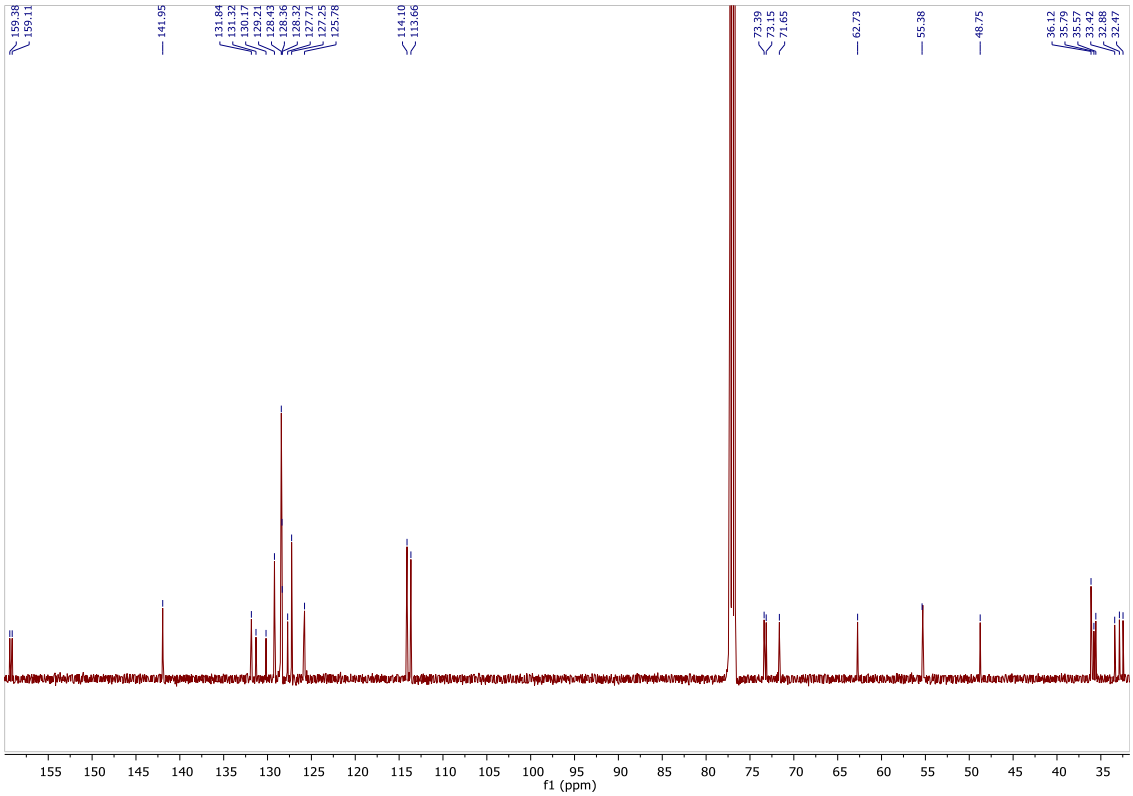

Ph
O
H
Ph
O
H
OMe
OMe
143
13.36
6.28
1.03
1.08
1.00
1.04
0.99
1.08
3.11
2.93
4.16
3.28
1.01
5.24
2.12
f1 (ppm)


159.15
158.45
142.06
133.13
132.04
130.39
129.67
128.46
128.43
128.42
127.20
126.84
125.88
113.77
113.35
75.75
72.86
71.97
66.70
55.27
54.97
51.55
37.49
36.98
35.64
33.57
32.80
32.42
f1 (ppm)

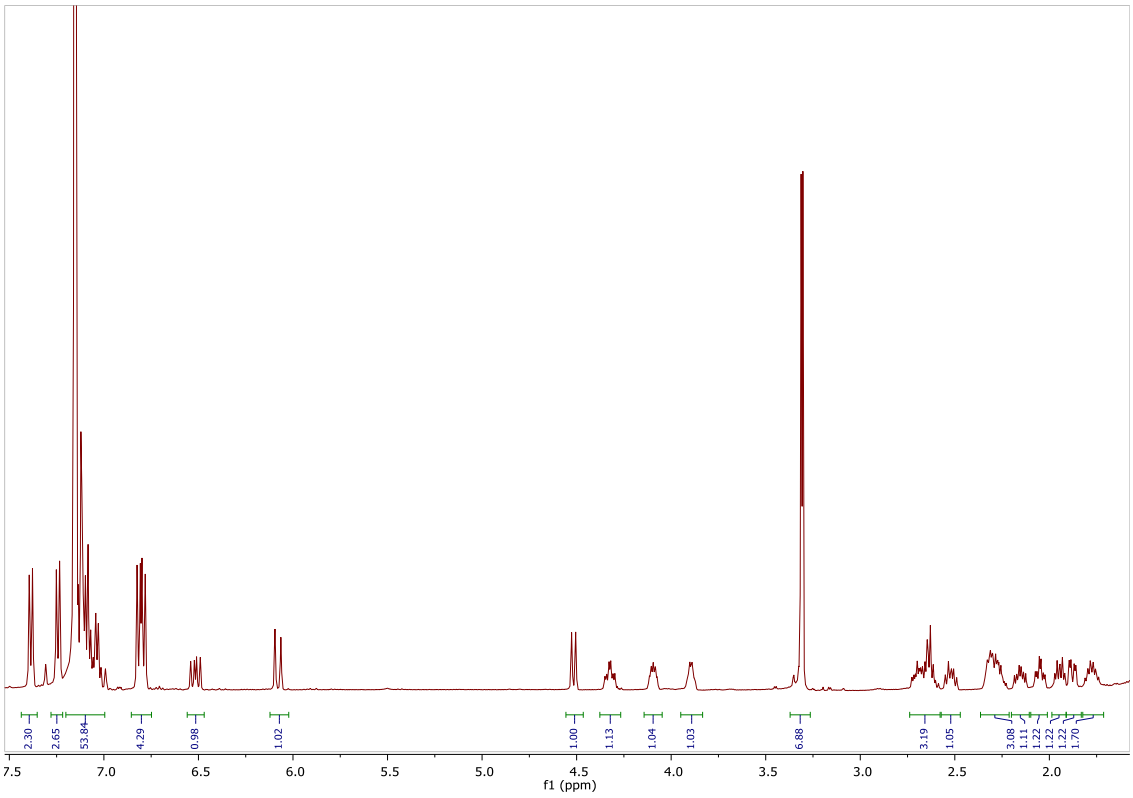

f2 (ppm)
f1 (ppm)

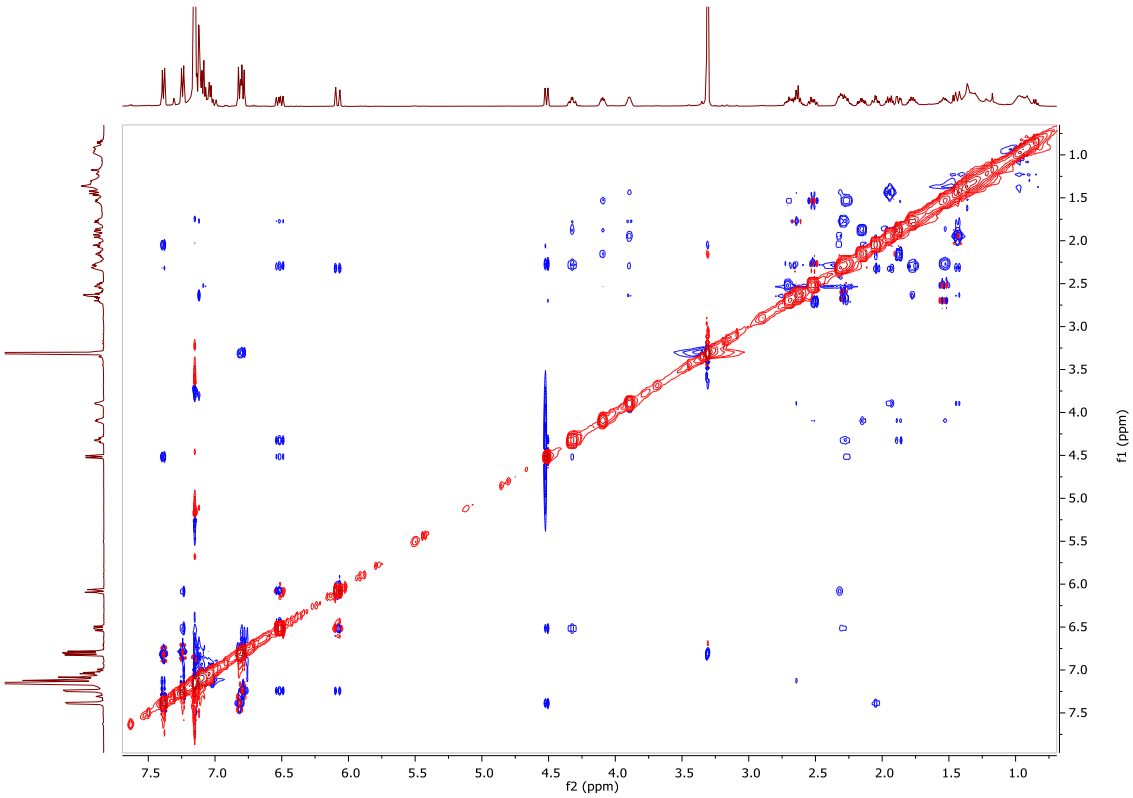

f1 (ppm)

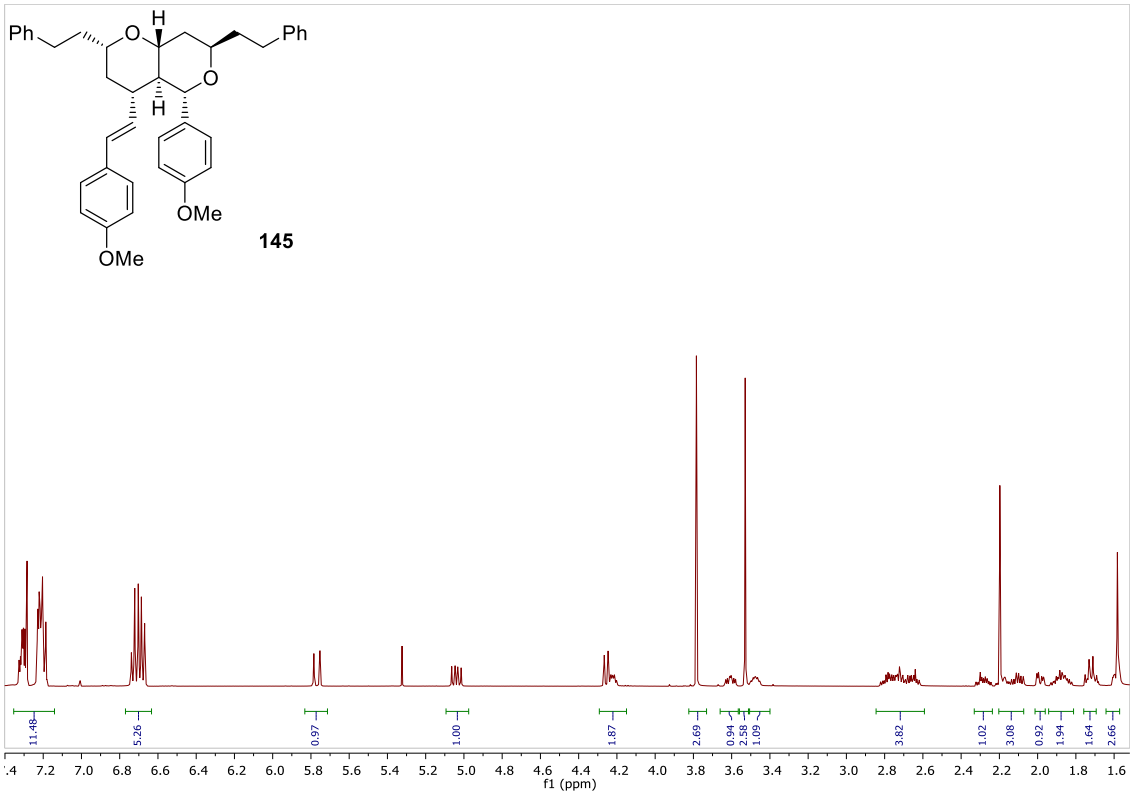

Ph
O
H
Ph
O
H
OMe
OMe
144
17.90
4.03
1.00
1.01
1.00
2.02
1.02
6.34
4.16
4.29
4.99
0.95
f1 (ppm)

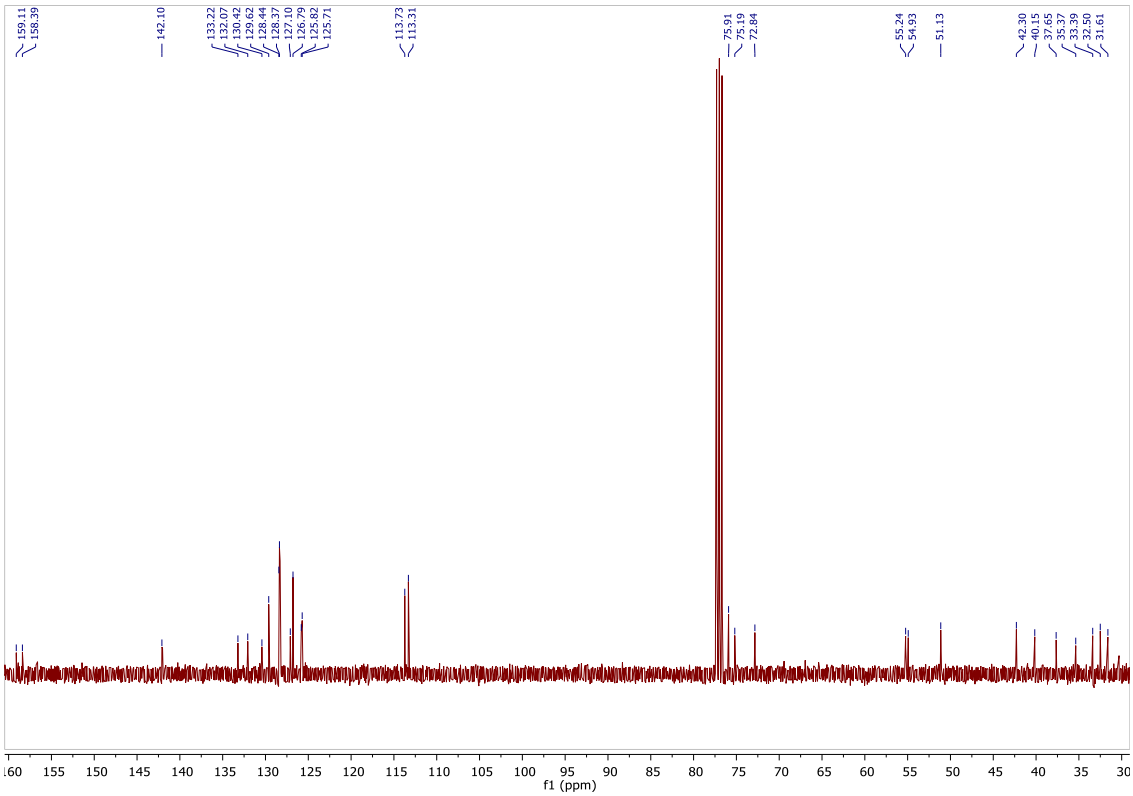

159.38
159.11
141.95
131.84
131.32
130.17
129.21
128.43
128.36
128.32
127.71
127.25
125.78
114.10
113.66
73.39
73.15
71.65
62.73
55.38
48.75
36.12
35.79
35.57
33.42
32.88
32.47
f1 (ppm)

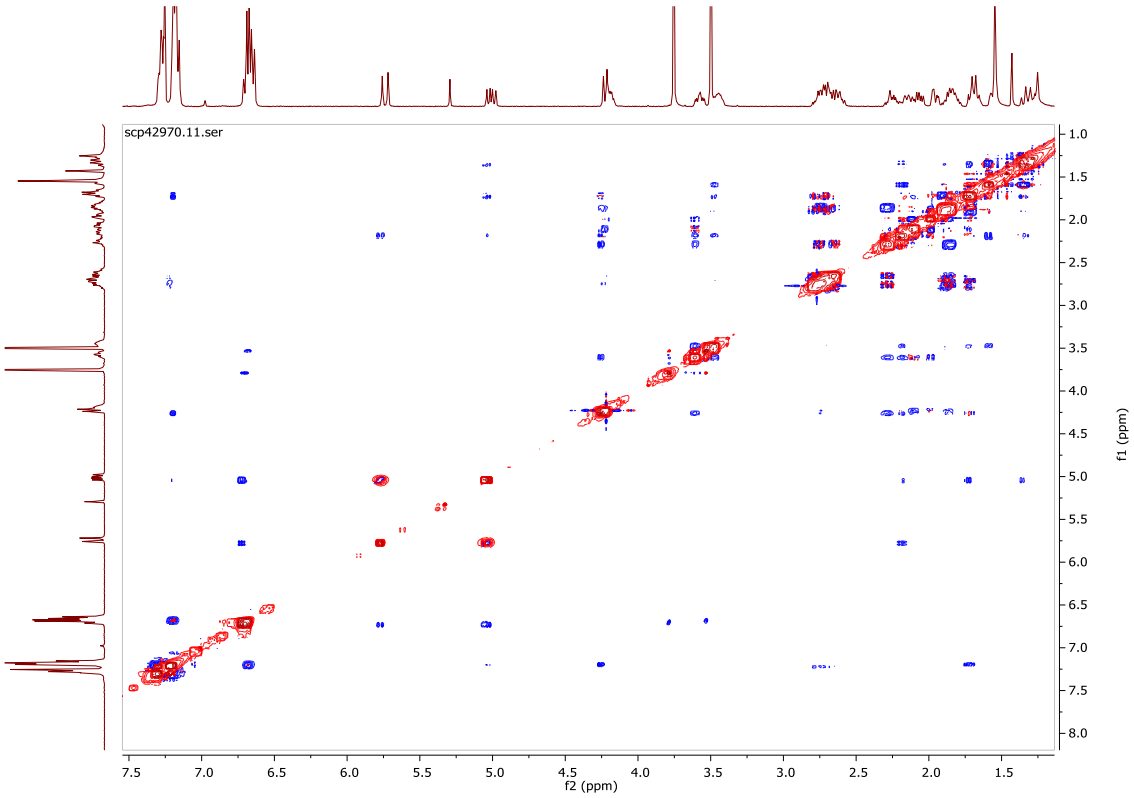
Benzene-d_6

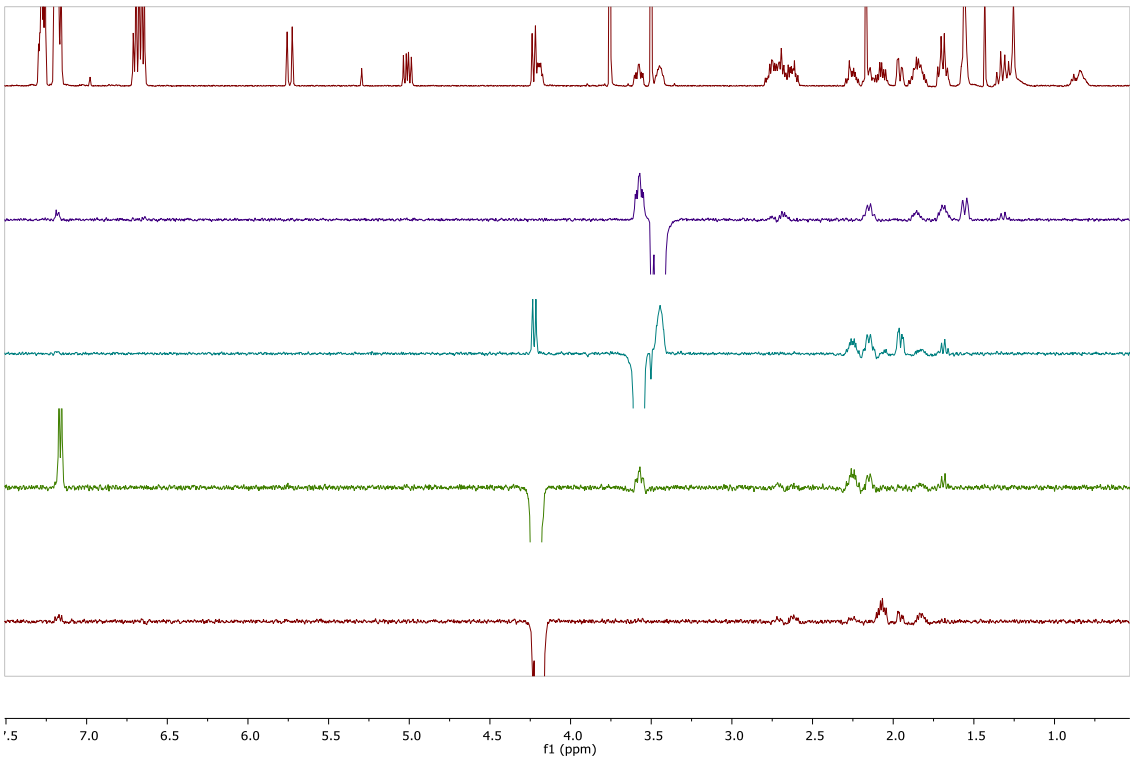

2.30
2.65
53.84
4.29
0.98
1.02
1.00
1.13
1.04
1.03
6.88
3.19
1.05
3.08
1.11
1.22
1.22
1.22
1.70
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

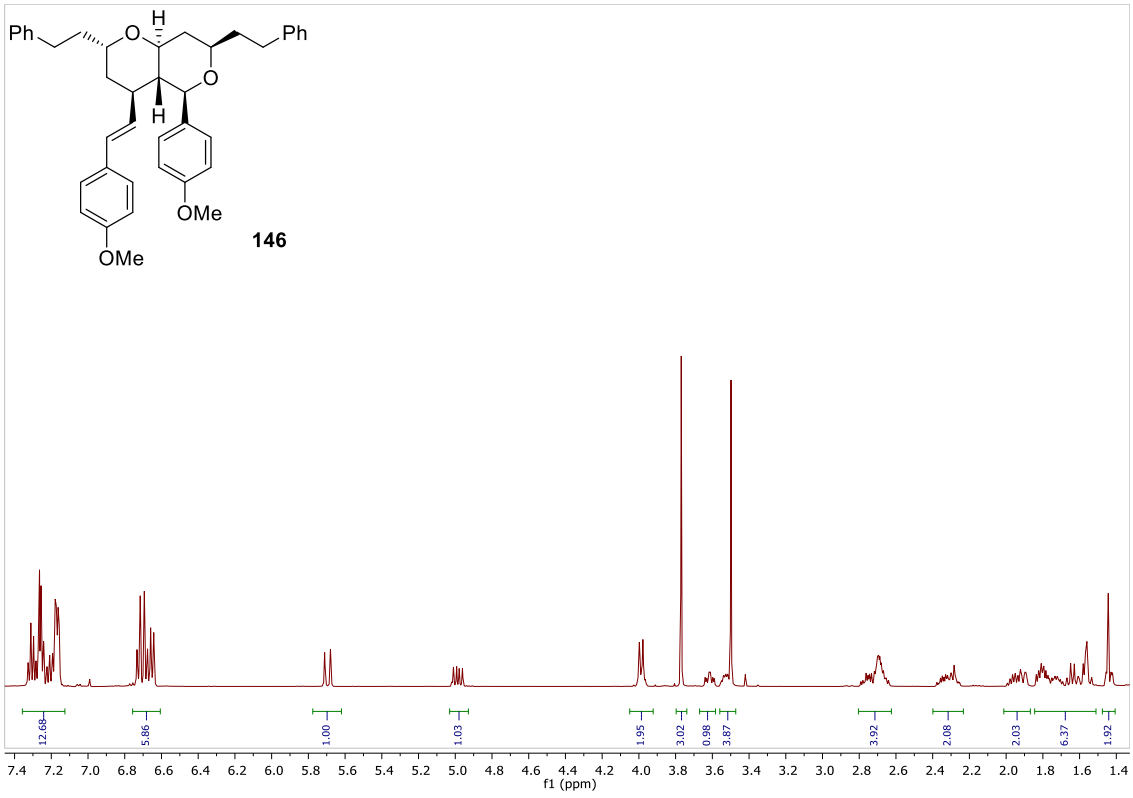

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)


Ph
O
H
Ph
O
H
OMe
OMe
145
11.48
5.26
0.97
1.00
1.87
2.69
0.94
2.58
1.09
3.82
1.02
3.08
0.92
1.94
1.64
2.66
f1 (ppm)

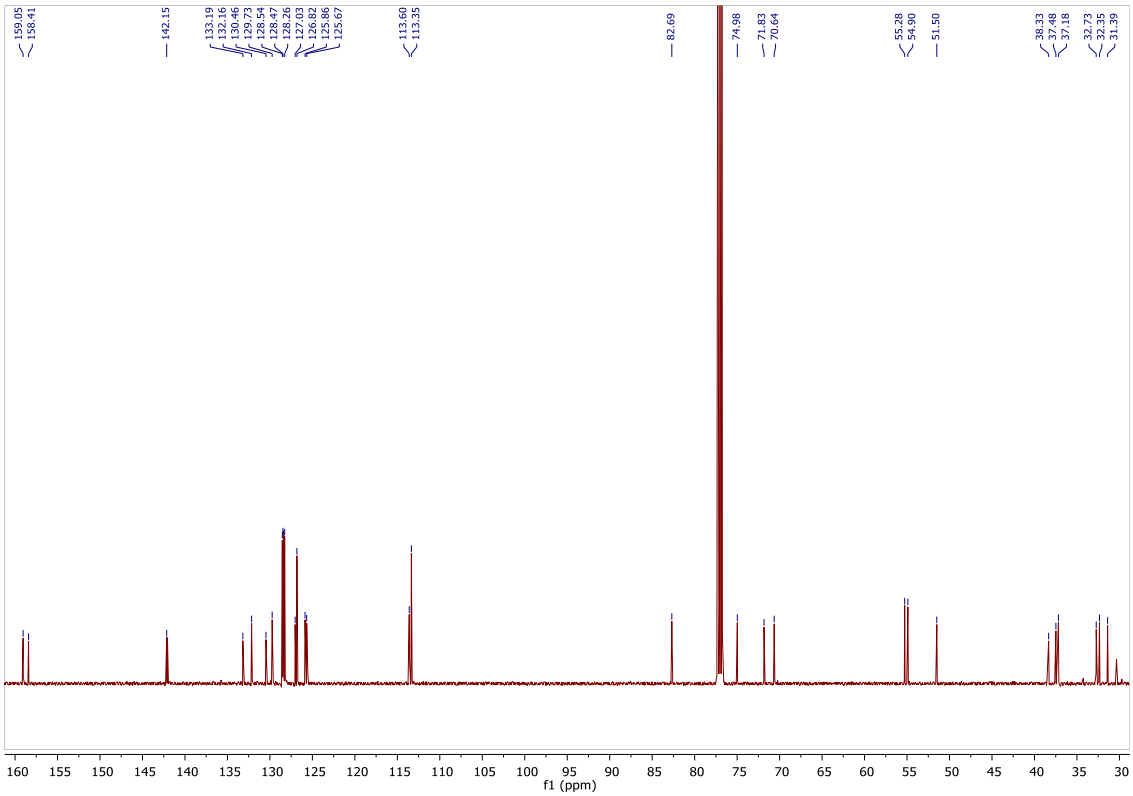

159.11
158.39
142.10
133.22
132.07
130.42
129.62
128.44
128.27
127.10
126.79
125.82
125.71
113.73
113.31
75.91
75.19
72.84
55.24
54.93
51.13
42.30
40.15
37.65
35.37
33.30
32.90
31.61
f1 (ppm)

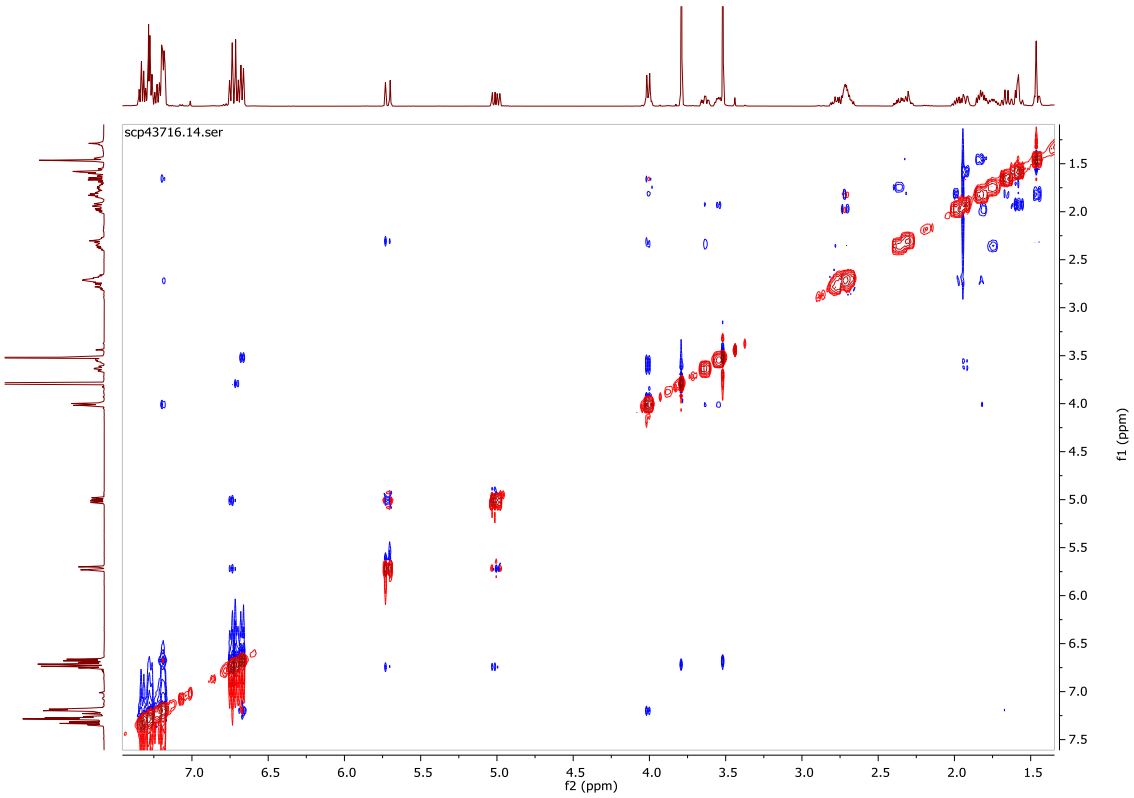

scp42970.11.ser
f2 (ppm)
f1 (ppm)

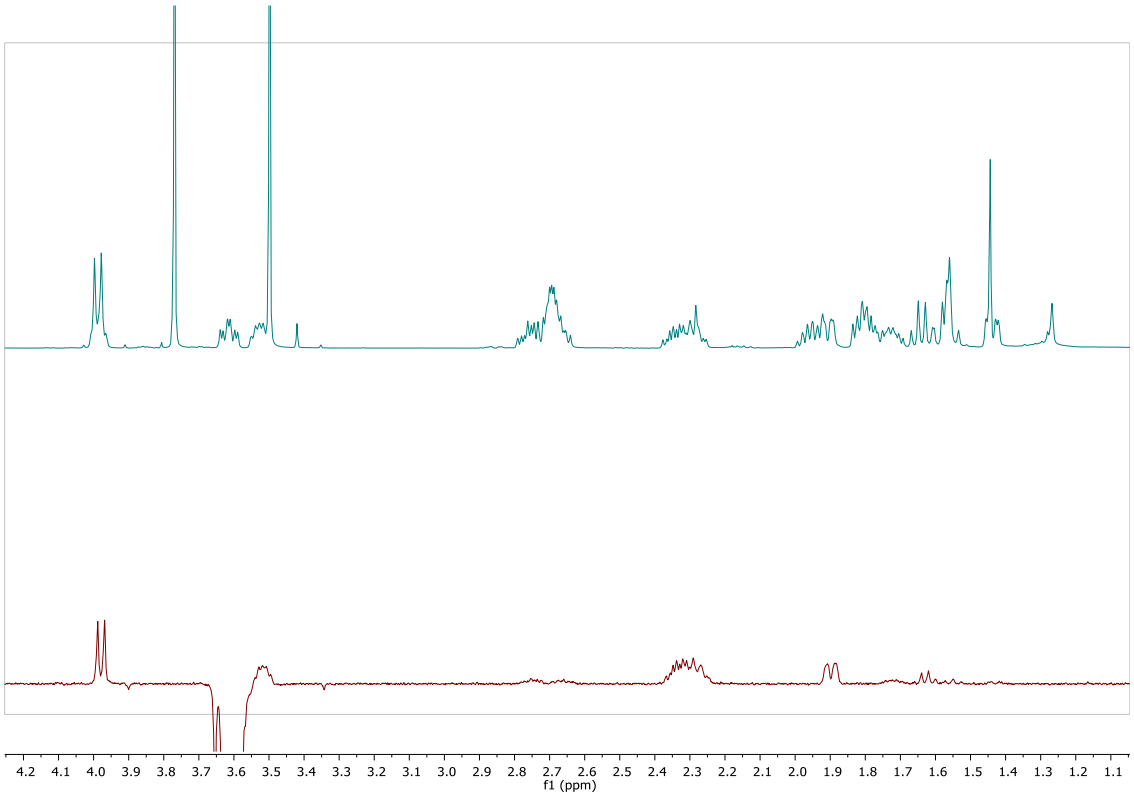

f1 (ppm)

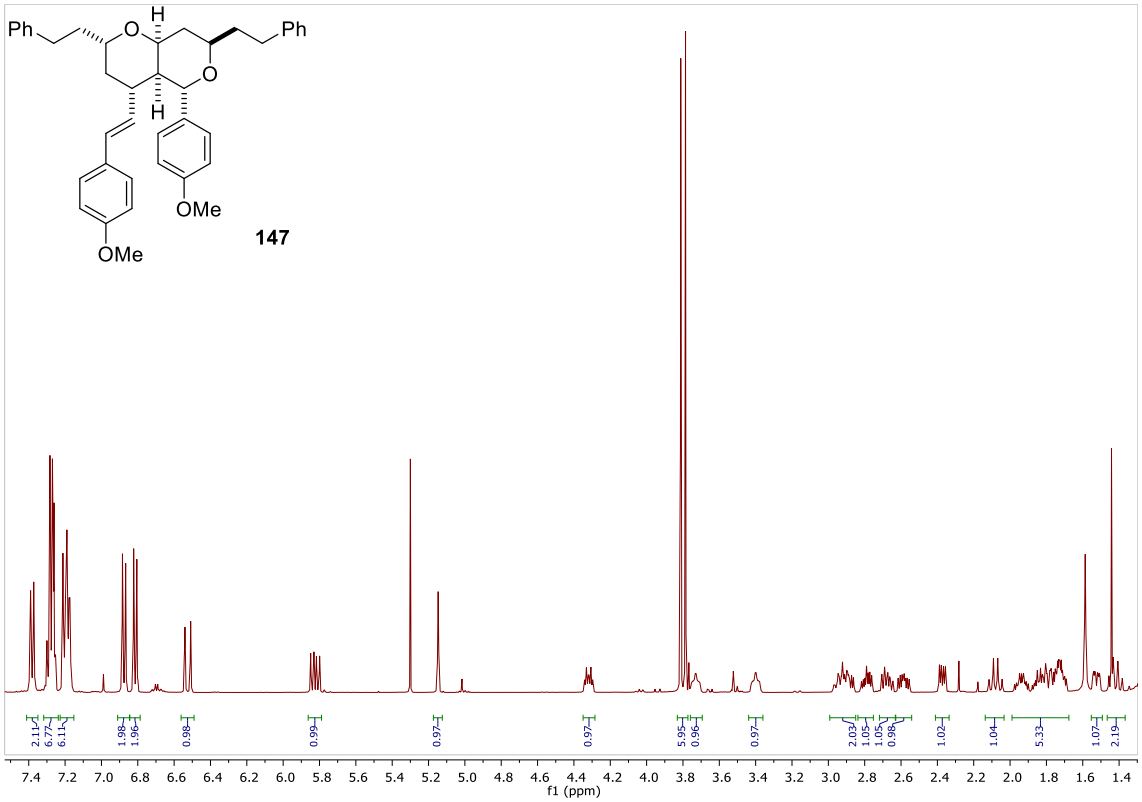

Ph
O
H
Ph
O
H
OMe
OMe
12.68
5.86
1.00
1.03
1.95
3.02
0.98
3.87
3.92
2.08
2.03
6.37
1.92
f1 (ppm)

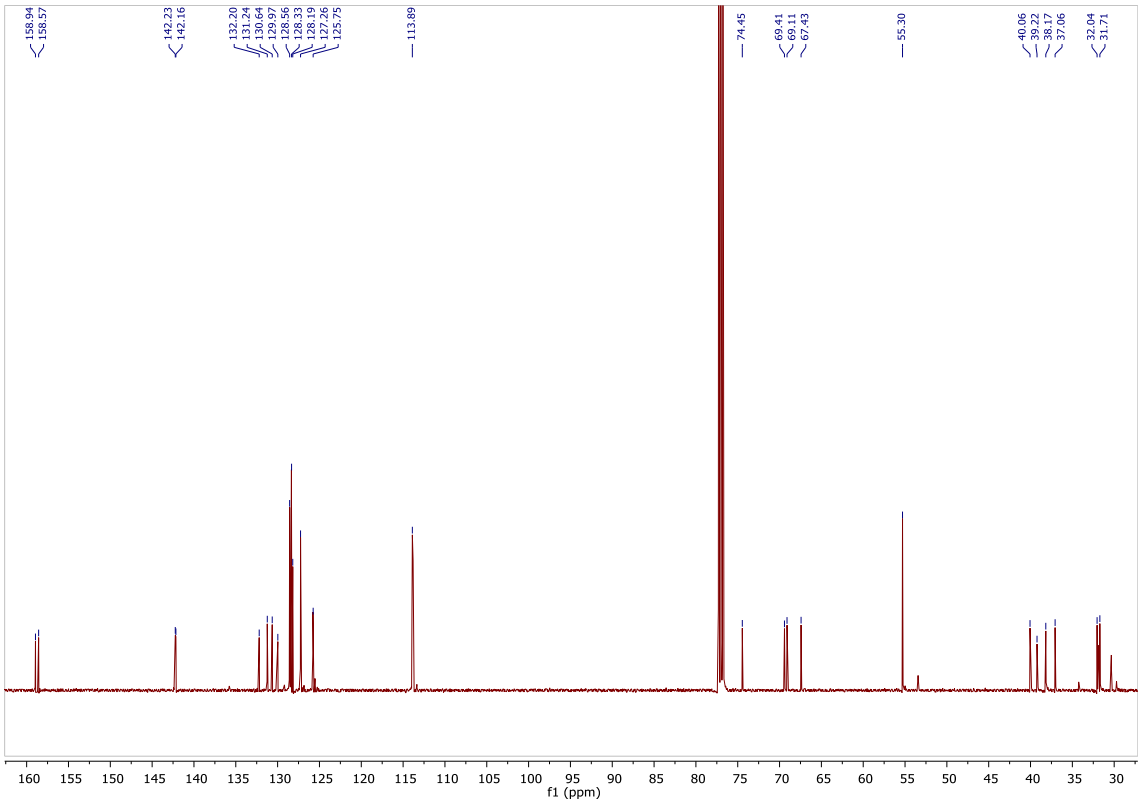
146


159.05
158.41
142.15
133.19
132.16
130.46
130.23
128.54
128.47
128.26
127.03
126.82
125.86
125.67
113.60
113.35
82.69
74.98
71.83
70.64
55.28
54.90
51.50
38.33
37.48
37.18
32.73
32.35
31.39
f1 (ppm)


scp43716.14.ser
f2 (ppm)
f1 (ppm)


f1 (ppm)


Ph
O
H
Ph
O
H
OMe
OMe
147
f1 (ppm)


158.94
158.57
142.23
142.16
132.20
131.24
130.64
129.97
128.56
128.33
128.19
127.26
125.75
113.89
74.45
69.41
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40.06
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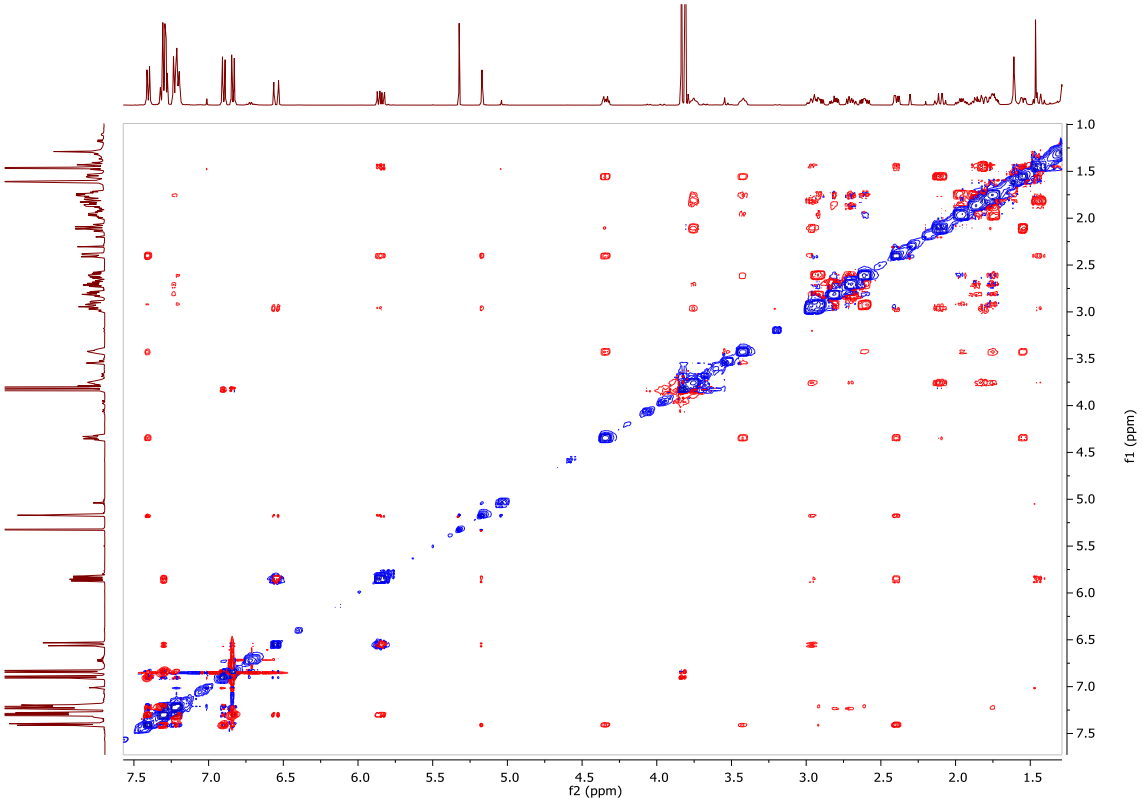
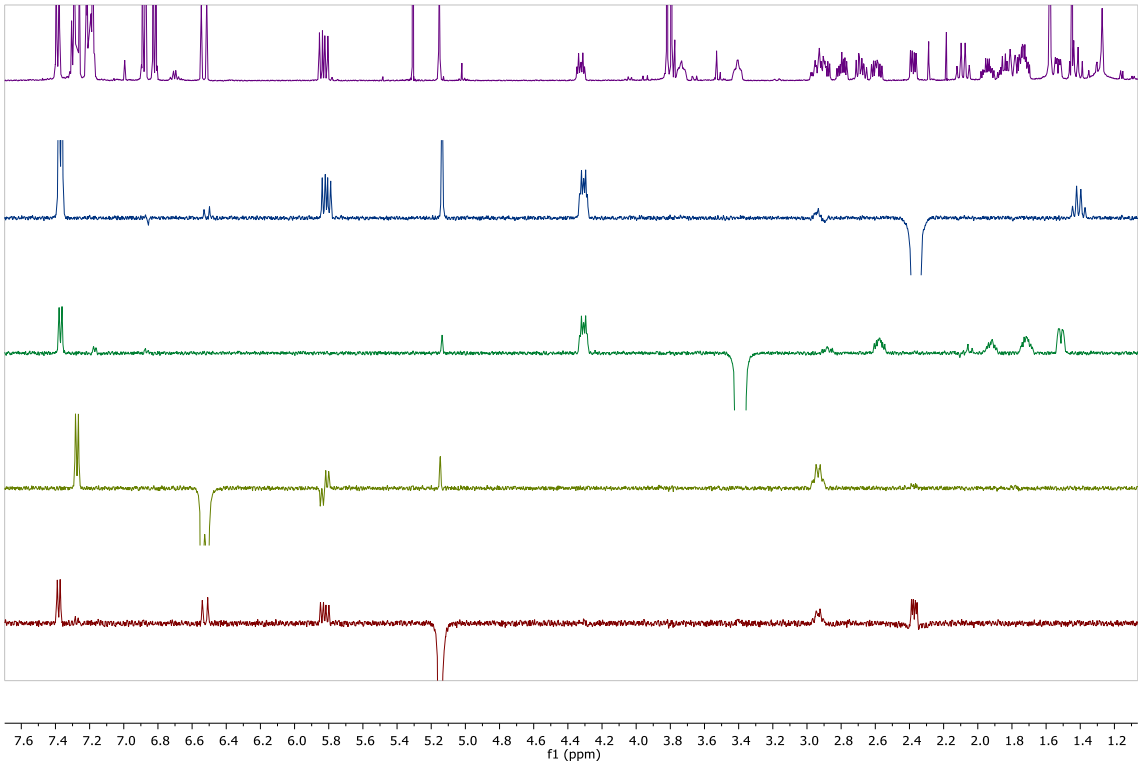
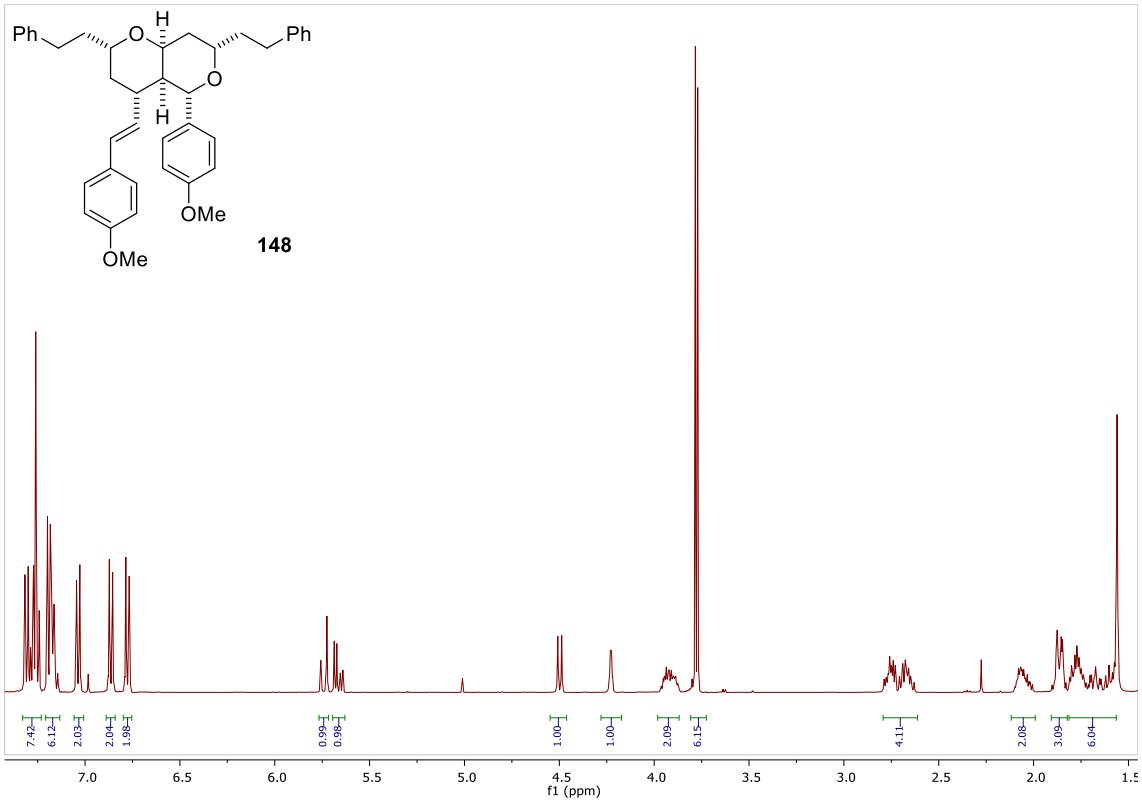
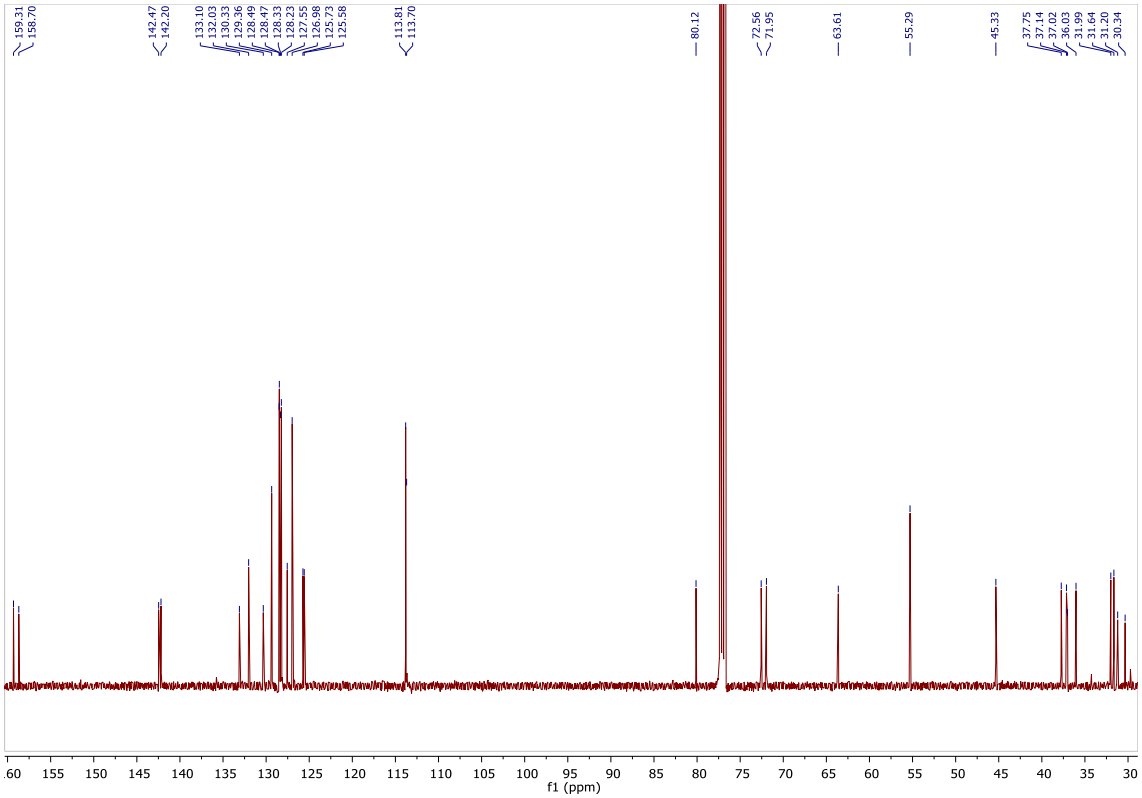
38.17
37.06
32.04
31.71
f1 (ppm)


f2 (ppm)
f1 (ppm)


f1 (ppm)


Ph
O
H
Ph
O
H
OMe
OMe
148
7.42
6.12
2.03
2.04
1.98
0.99
0.98
1.00
1.00
2.09
6.15
4.11
2.08
3.09
6.04
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)


159.31
158.70
142.47
142.20
133.10
132.03
130.33
129.36
128.49
128.47
128.33
128.23
127.55
126.98
125.73
125.58
113.81
113.70
80.12
72.56
71.95
63.61
55.29
45.33
37.75
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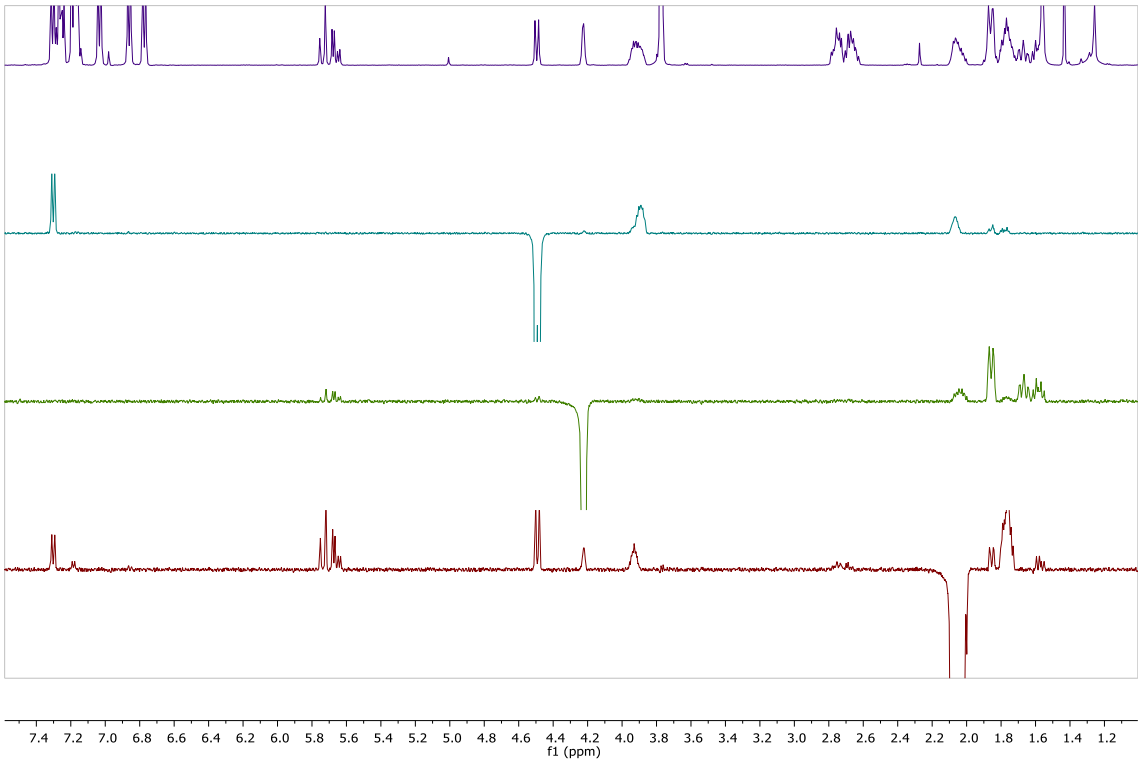
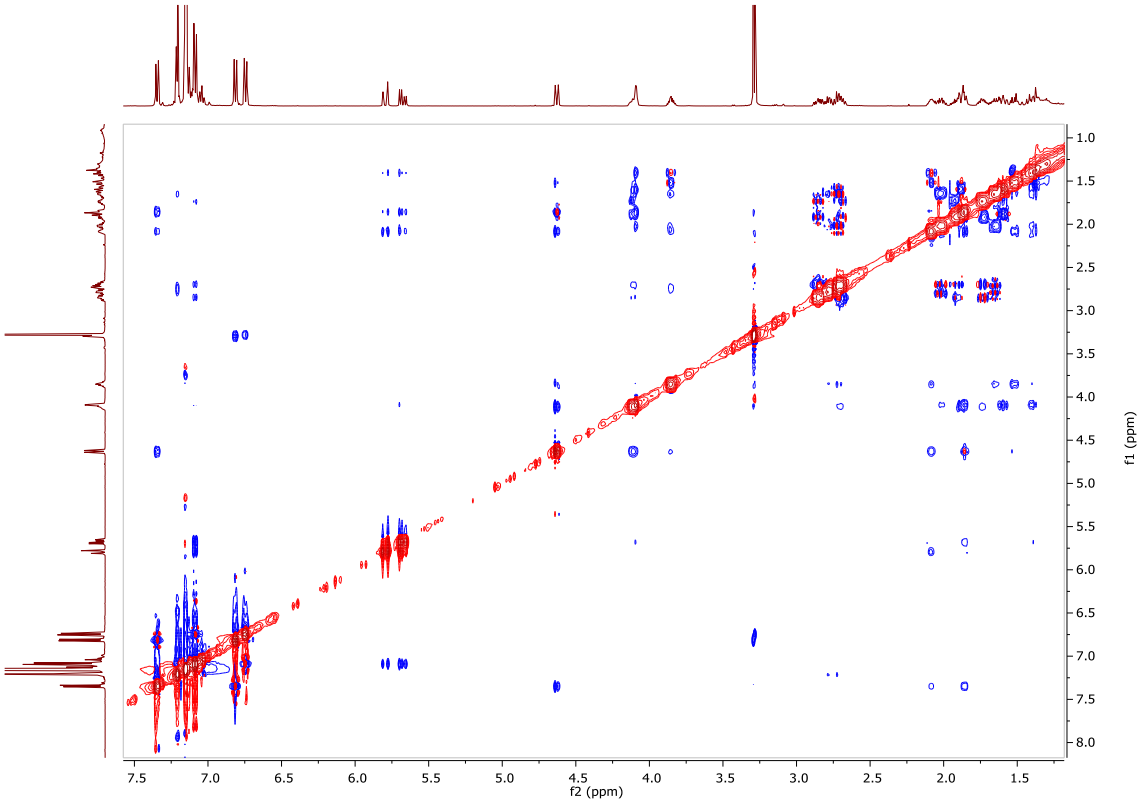
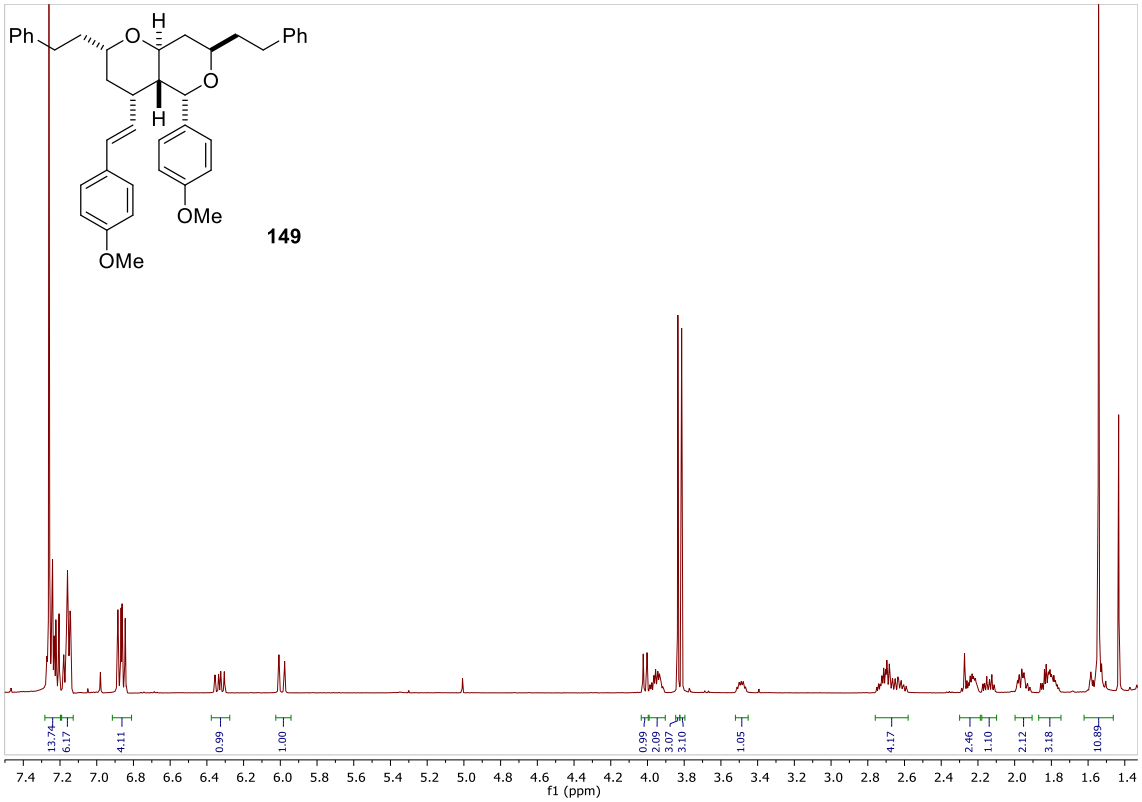
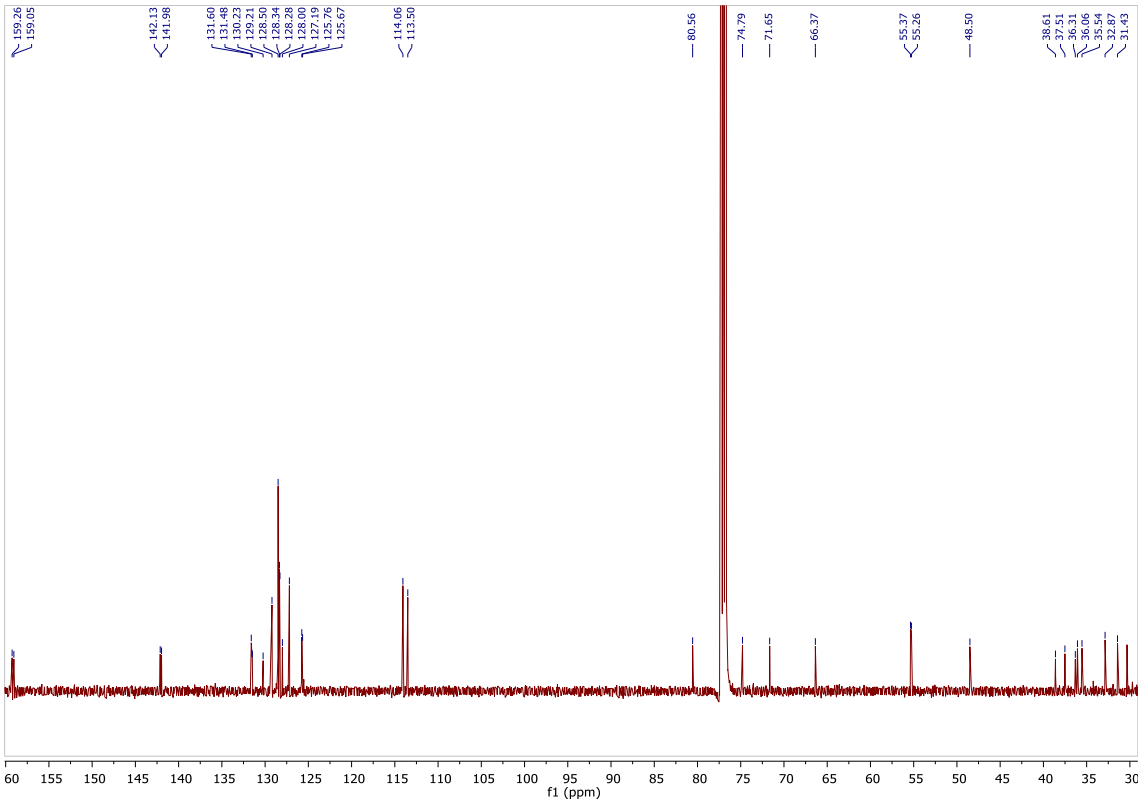
36.03
31.99
31.64
31.20
30.34
f1 (ppm)


7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)

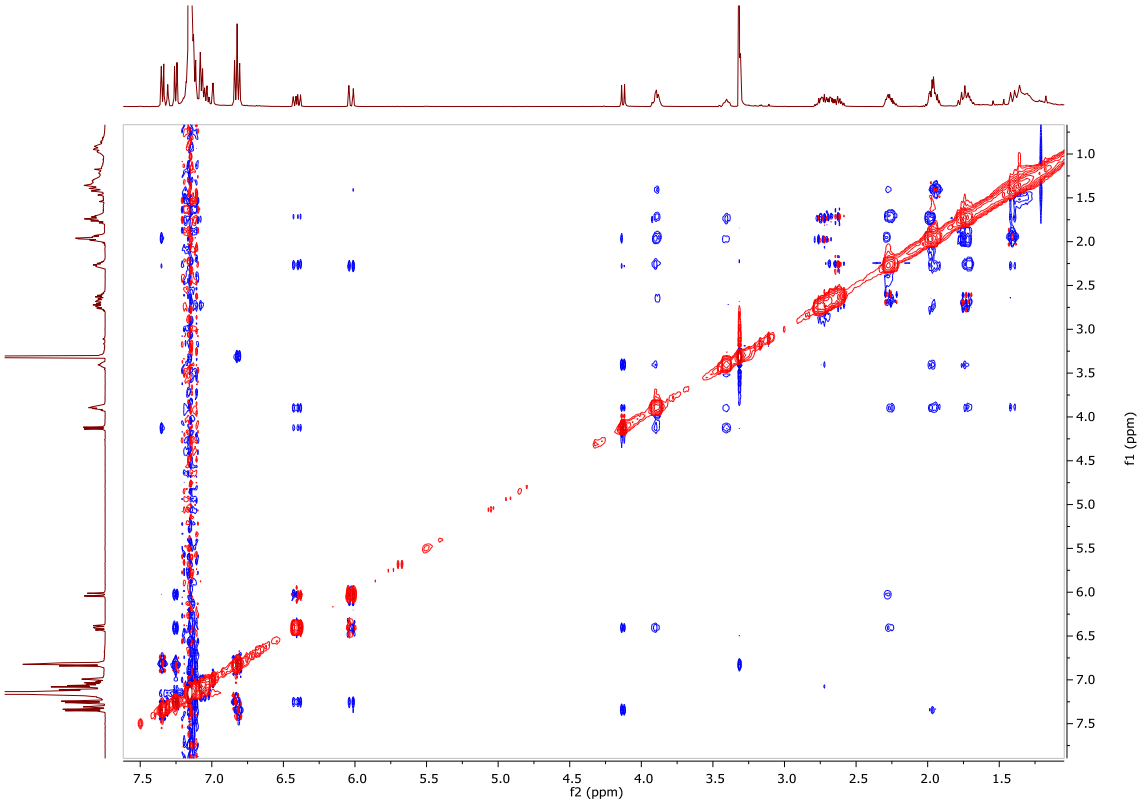
Benzene-d_6

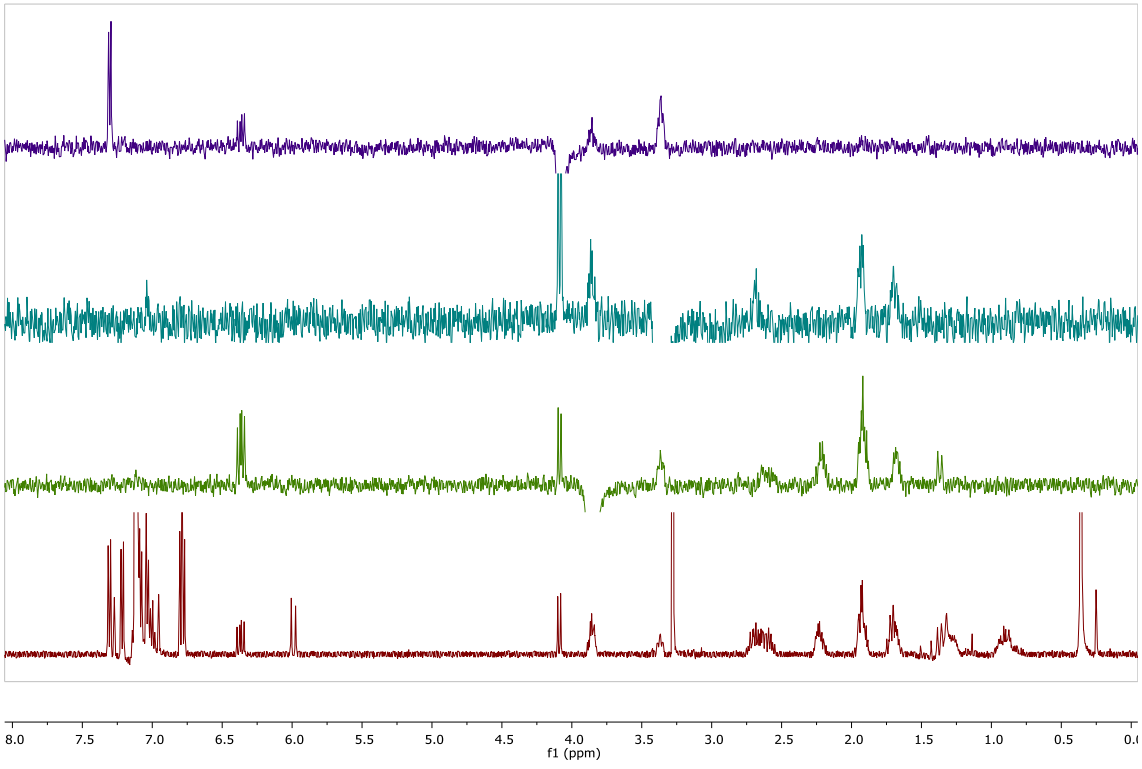

1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0
f1 (ppm)
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
f2 (ppm)

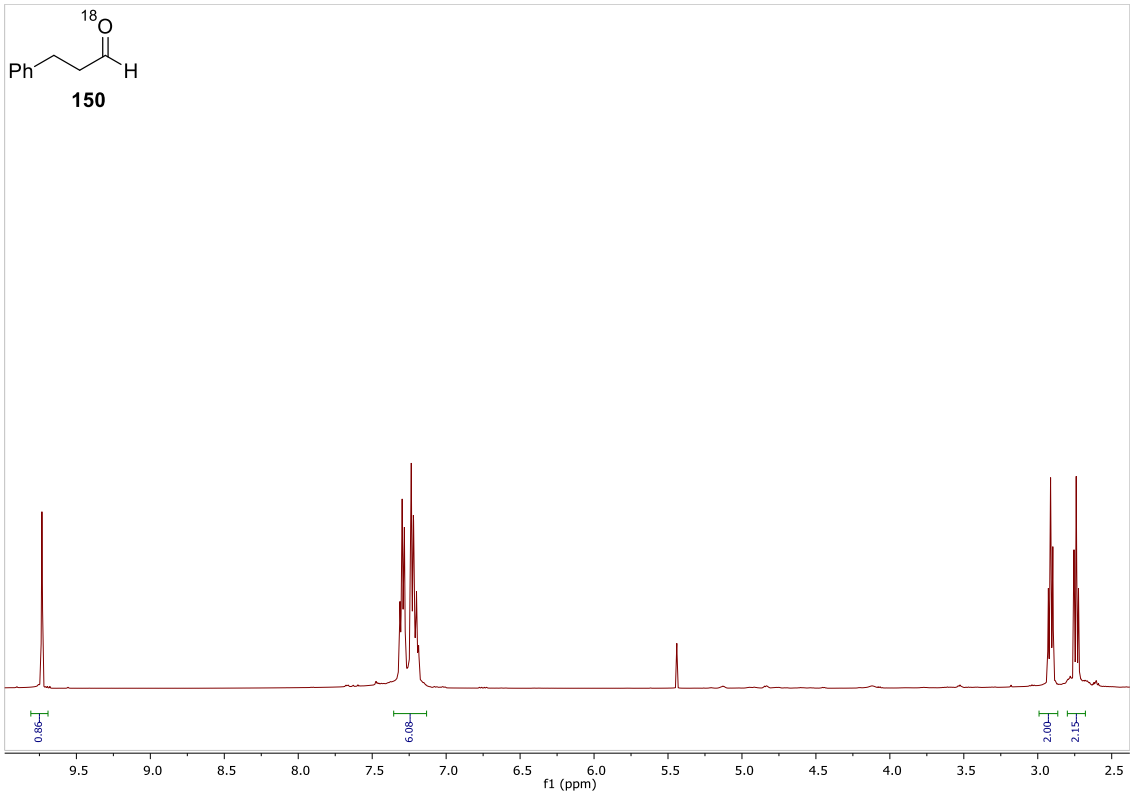

Ph
O
H
Ph
O
H
OMe
OMe
149
13.74
6.17
4.11
0.99
1.00
0.99
2.09
3.07
3.10
1.05
4.17
2.46
1.10
2.12
3.18
10.89
f1 (ppm)

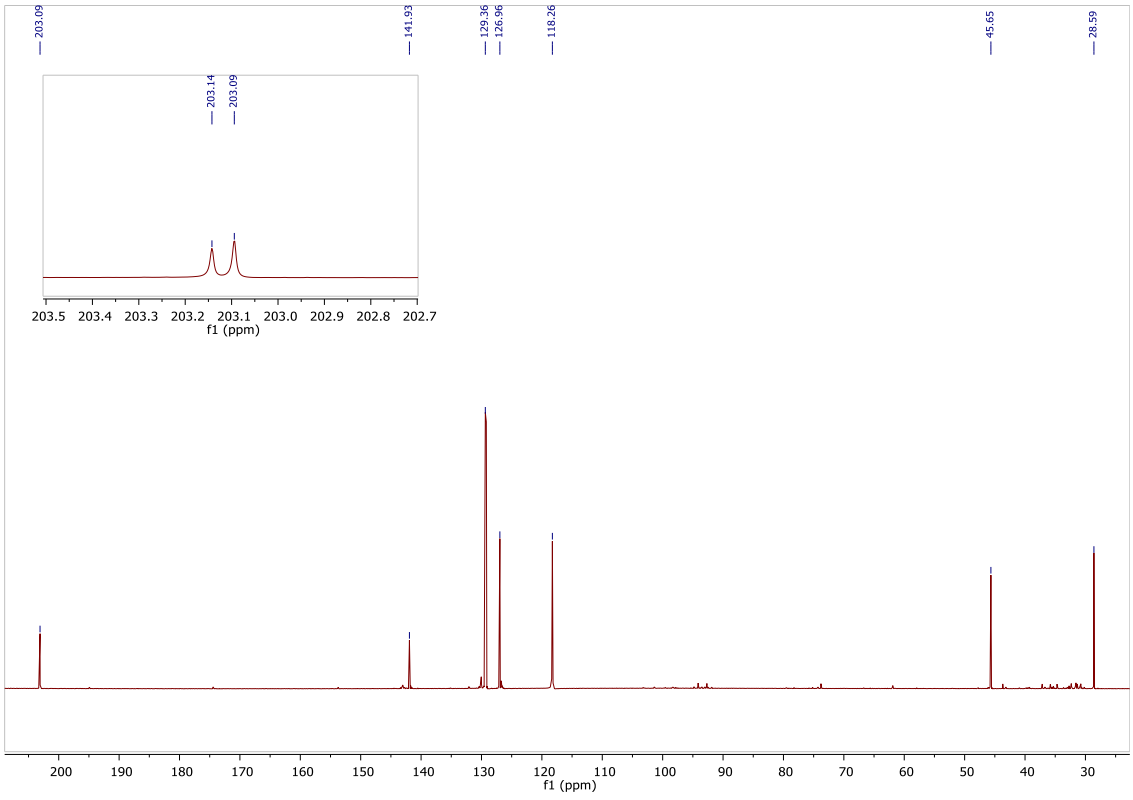

159.26
159.05
142.13
141.98
131.60
131.48
130.23
129.21
128.50
128.34
128.28
128.00
127.19
125.76
125.67
114.06
113.50
80.56
74.79
71.65
66.37
55.37
55.26
48.50
38.61
37.51
36.31
36.06
35.54
32.87
31.43
f1 (ppm)

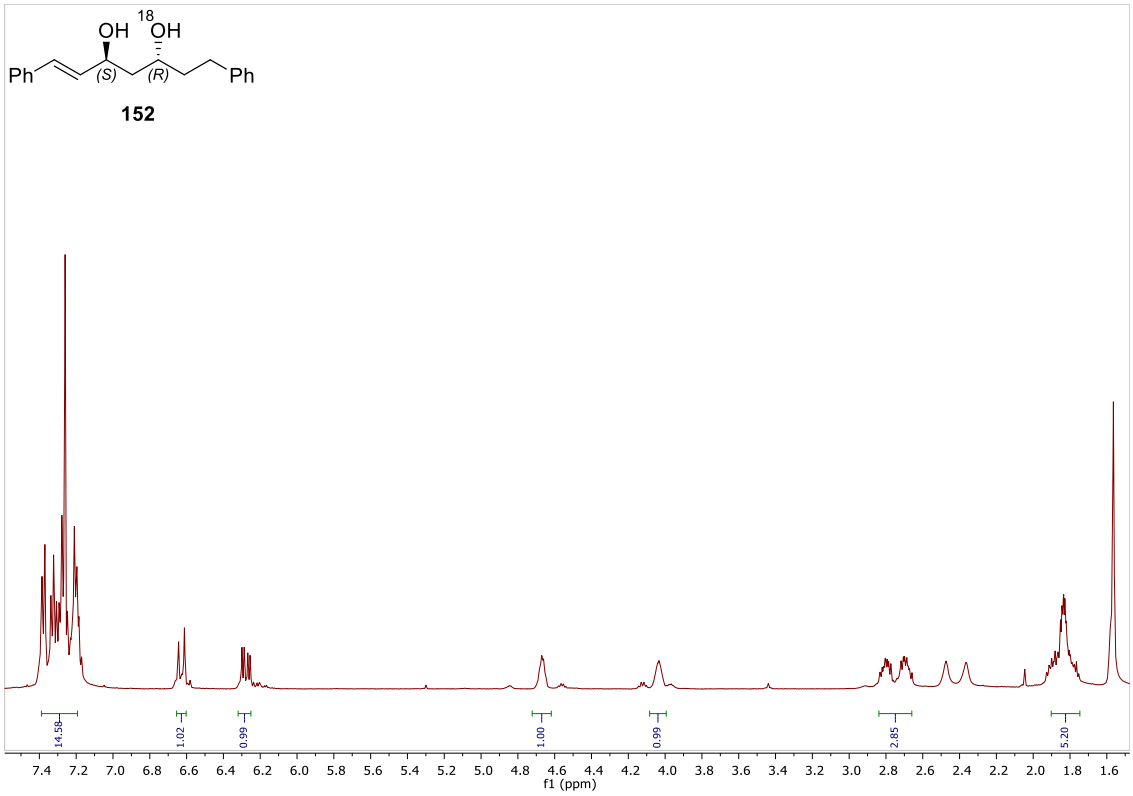
Benzene-d_6

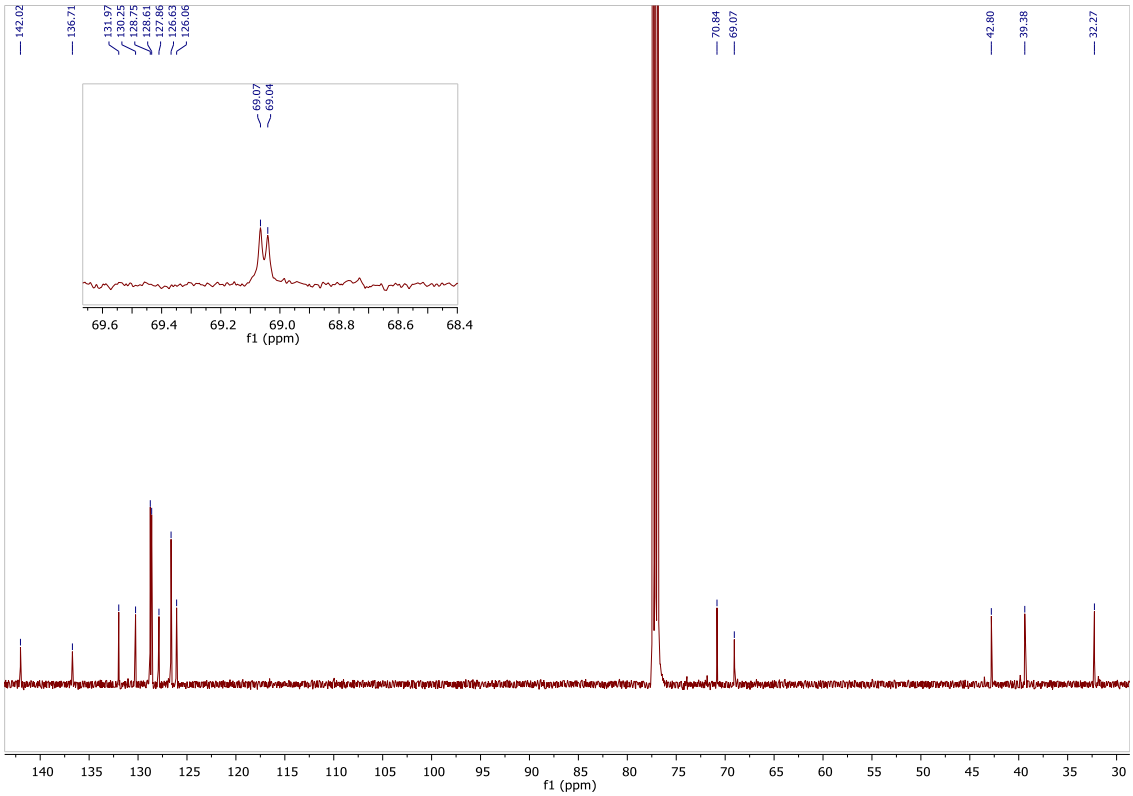

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)

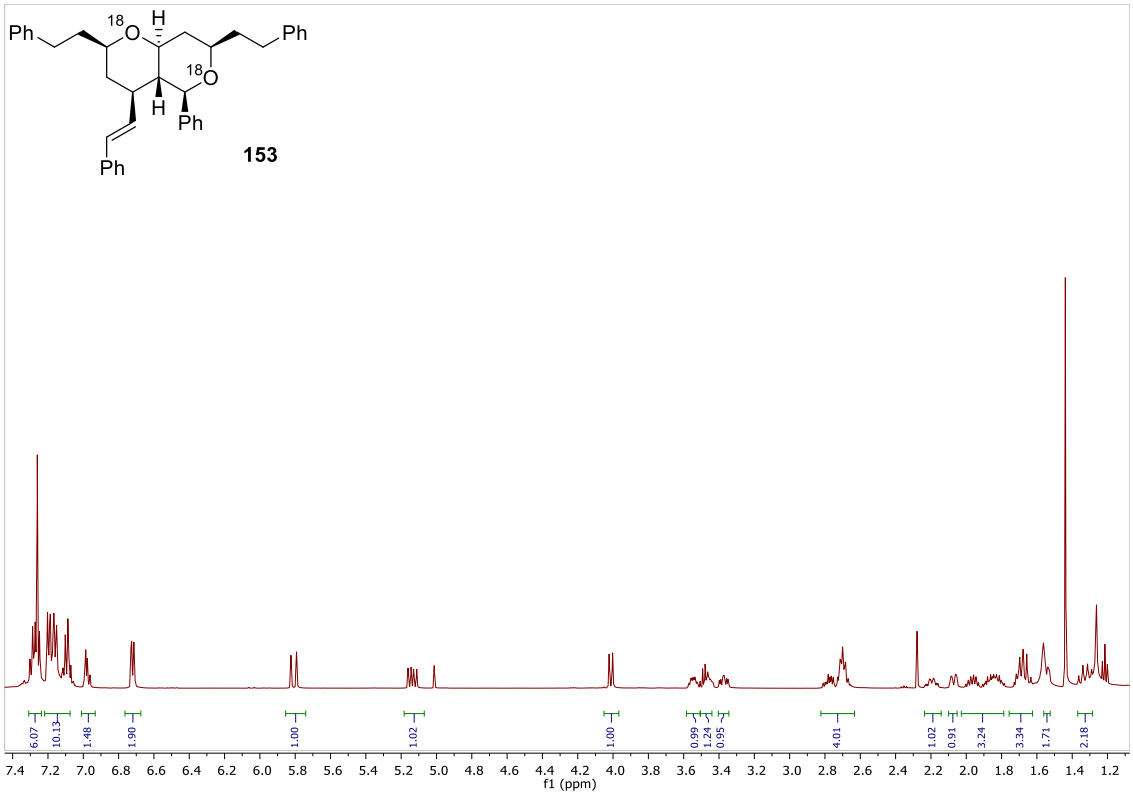

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

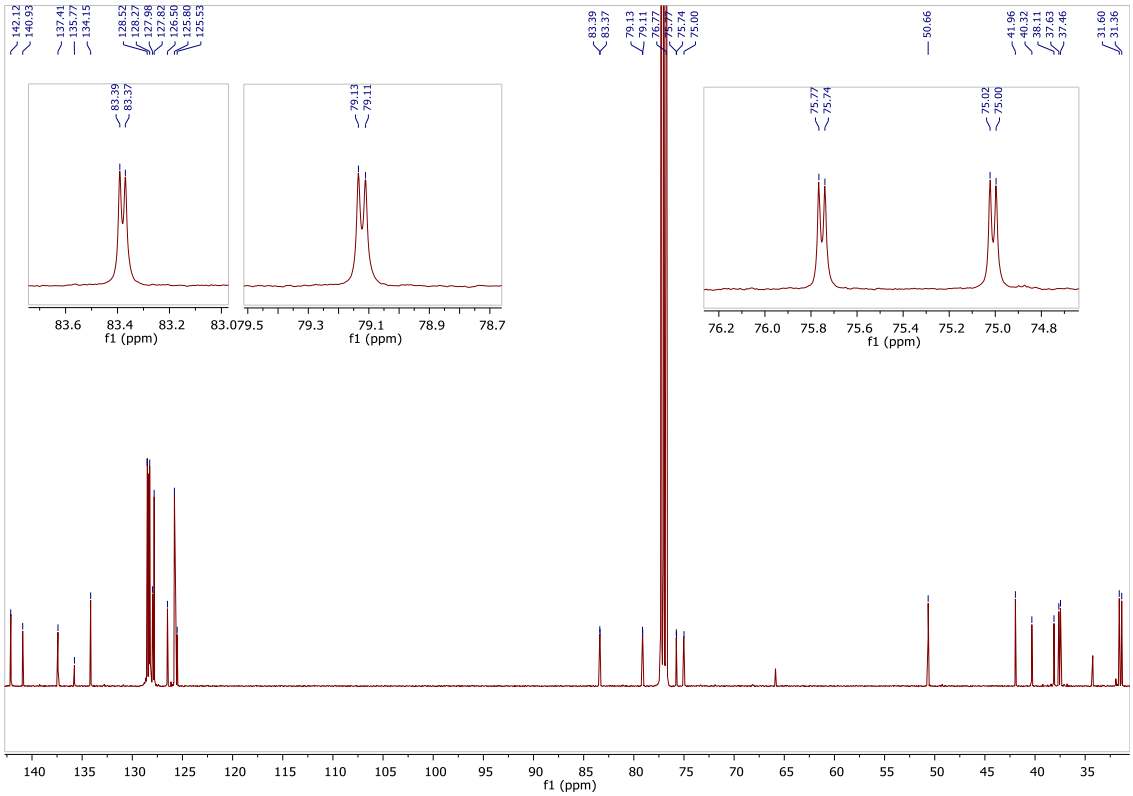

18
O
Ph
H
150
0.86
6.08
2.00
2.15
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5
f1 (ppm)

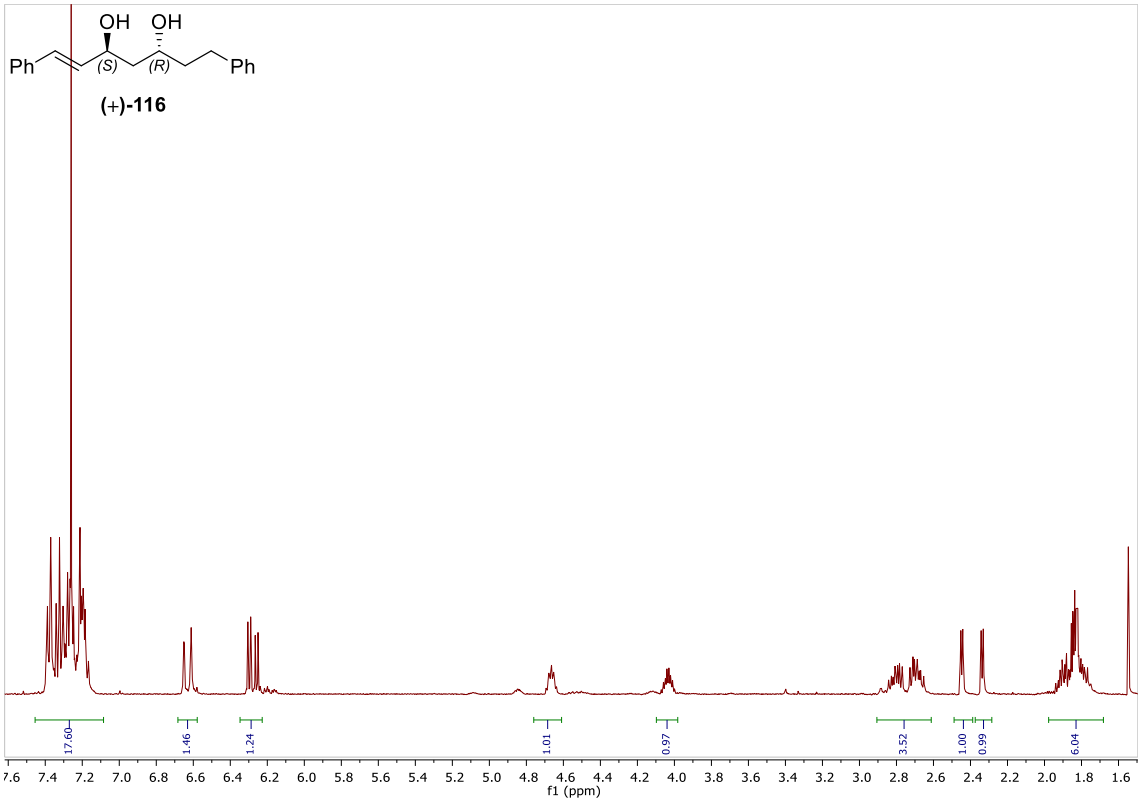

203.09
141.93
129.36
126.96
118.26
45.65
28.59
203.14
203.09
203.5 203.4 203.3 203.2 203.1 203.0 202.9 202.8 202.7
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
f1 (ppm)

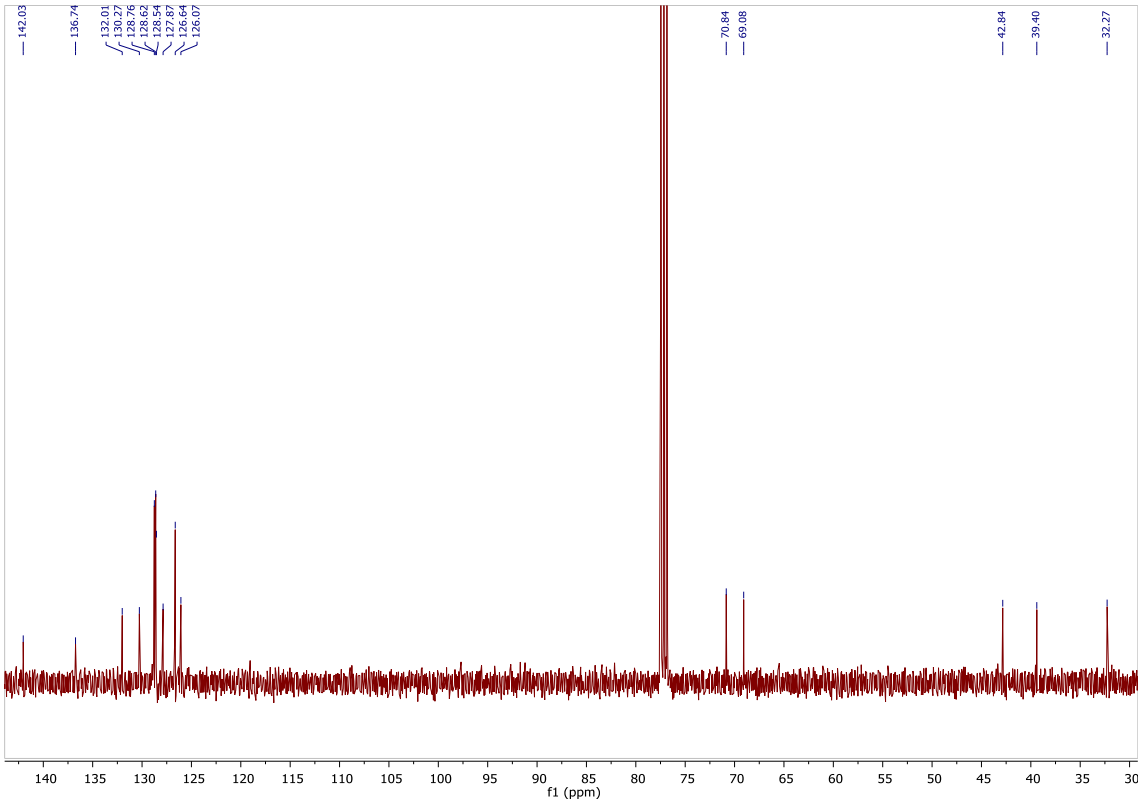

OH
18
OH
Ph
(S)
(R)
Ph
152
14.58
1.02
0.99
1.00
0.99
2.85
5.20
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)

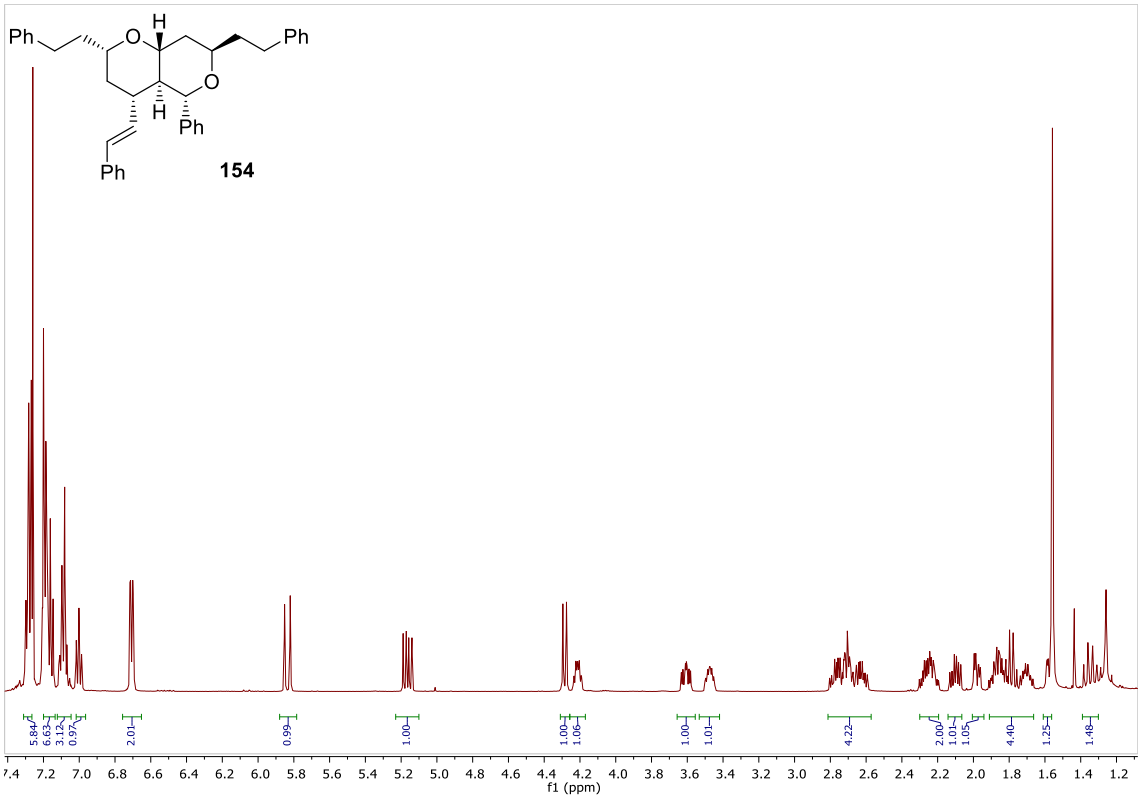

142.02
136.71
131.97
130.25
128.75
128.61
127.86
126.63
126.06
70.84
69.07
42.80
39.38
32.27
69.07
69.04
69.6 69.4 69.2 69.0 68.8 68.6 68.4
f1 (ppm)
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30
f1 (ppm)

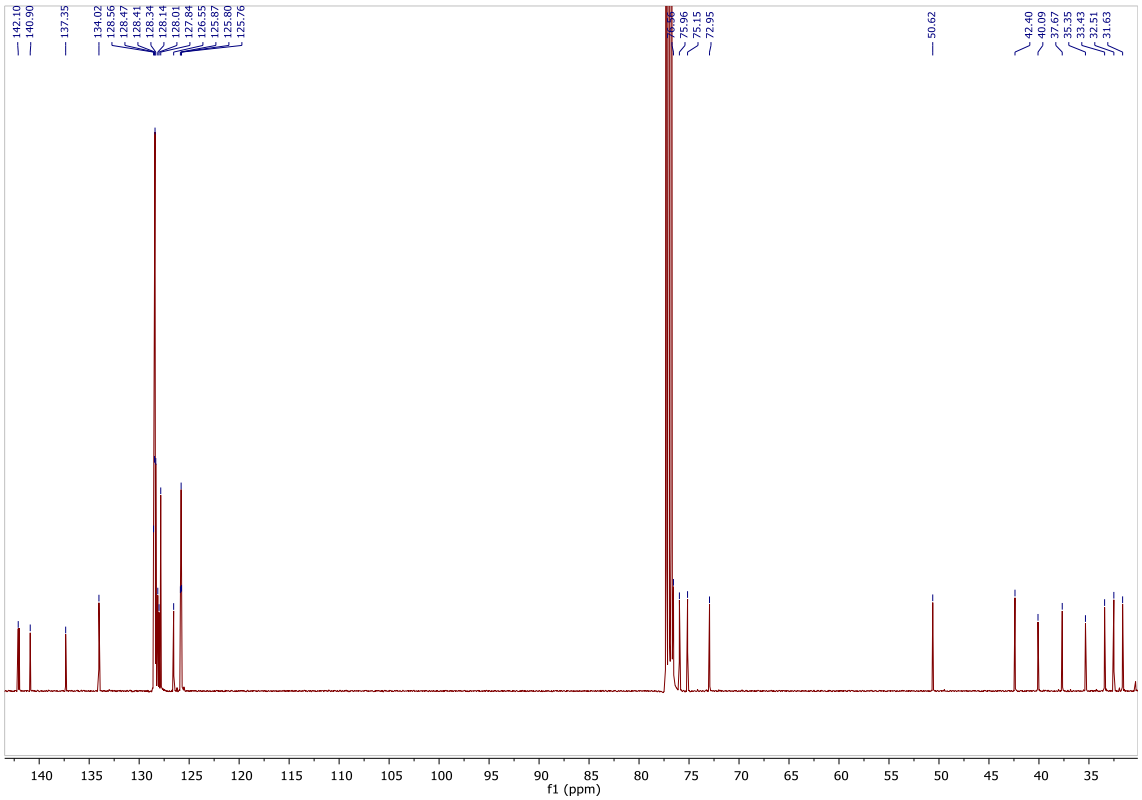

Ph
18
O
H
Ph
18
O
H
Ph
Ph
153
6.07
10.13
1.48
1.90
1.00
1.02
1.00
0.99
1.24
0.95
4.01
1.02
0.91
3.24
3.34
1.71
2.18
f1 (ppm)

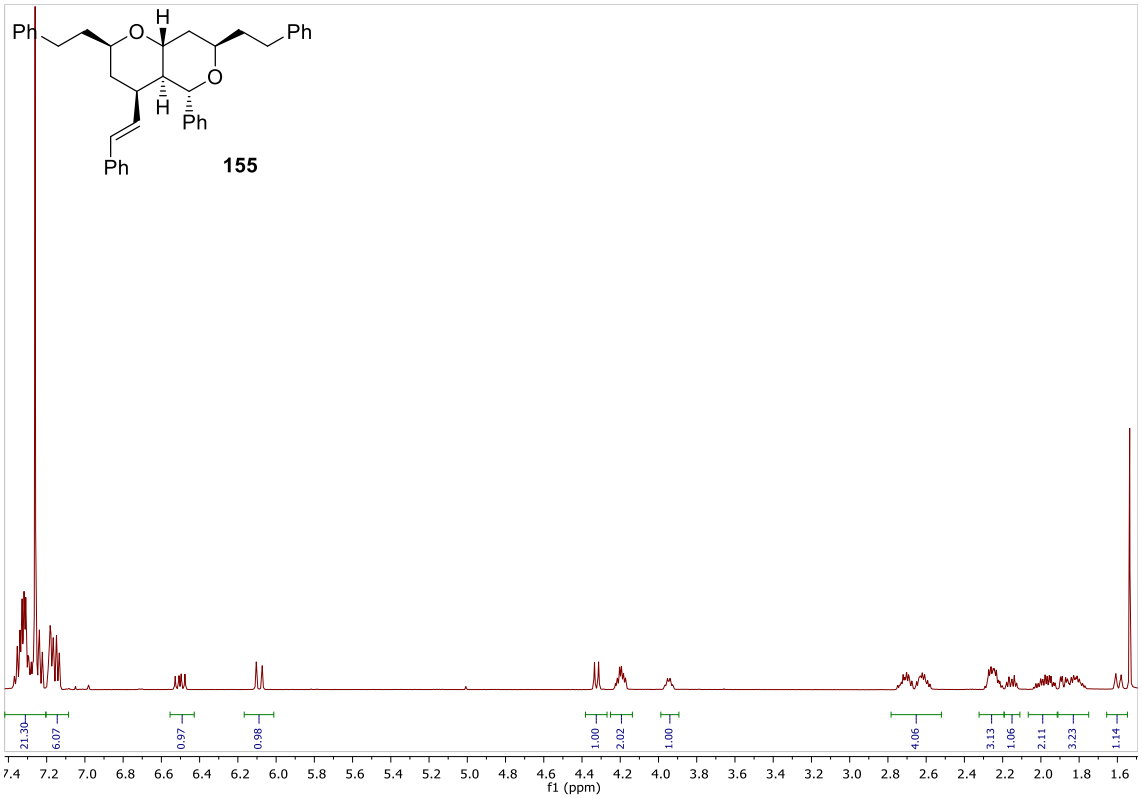

142.12
140.93
137.41
135.77
134.15
128.52
128.27
127.98
127.82
126.50
125.80
125.53
83.39
83.37
79.13
79.11
76.77
75.74
75.00
50.66
41.96
40.32
38.11
37.63
37.46
31.60
31.36
f1 (ppm)

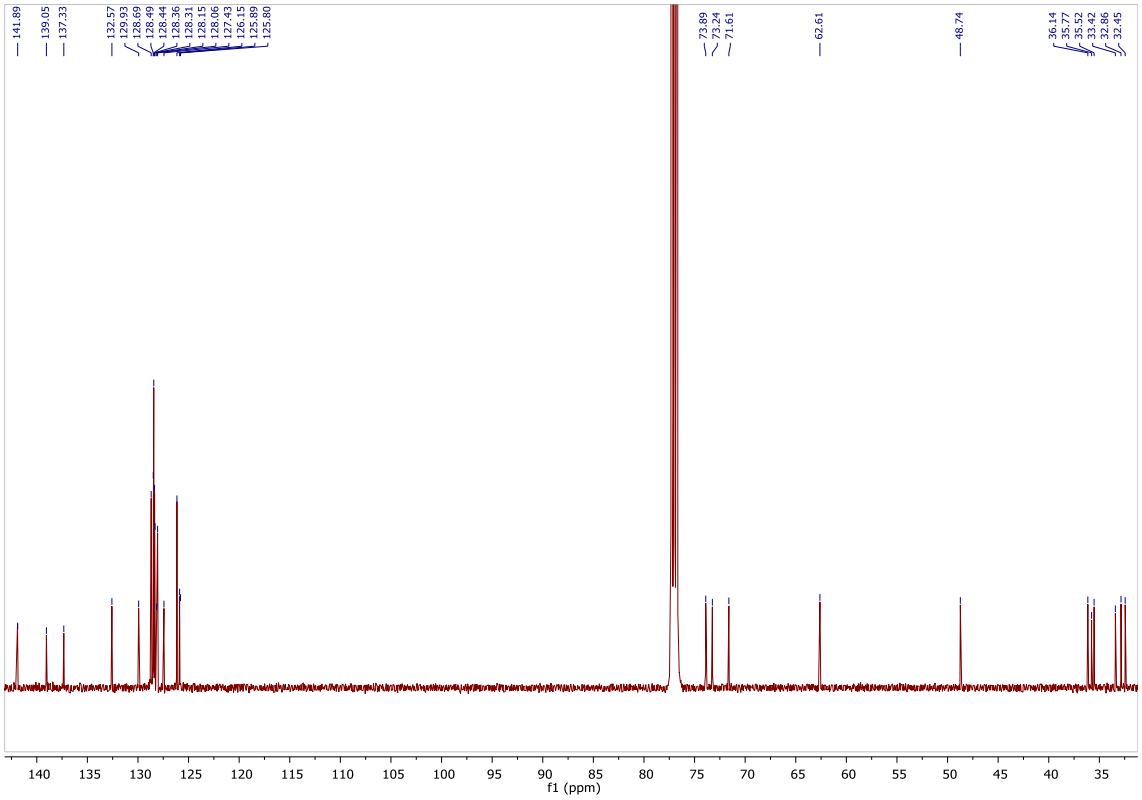

OH
OH
Ph
(S)
(R)
Ph
(+)-116
17.60
1.46
1.24
1.01
0.97
3.52
1.00
0.99
6.04
f1 (ppm)

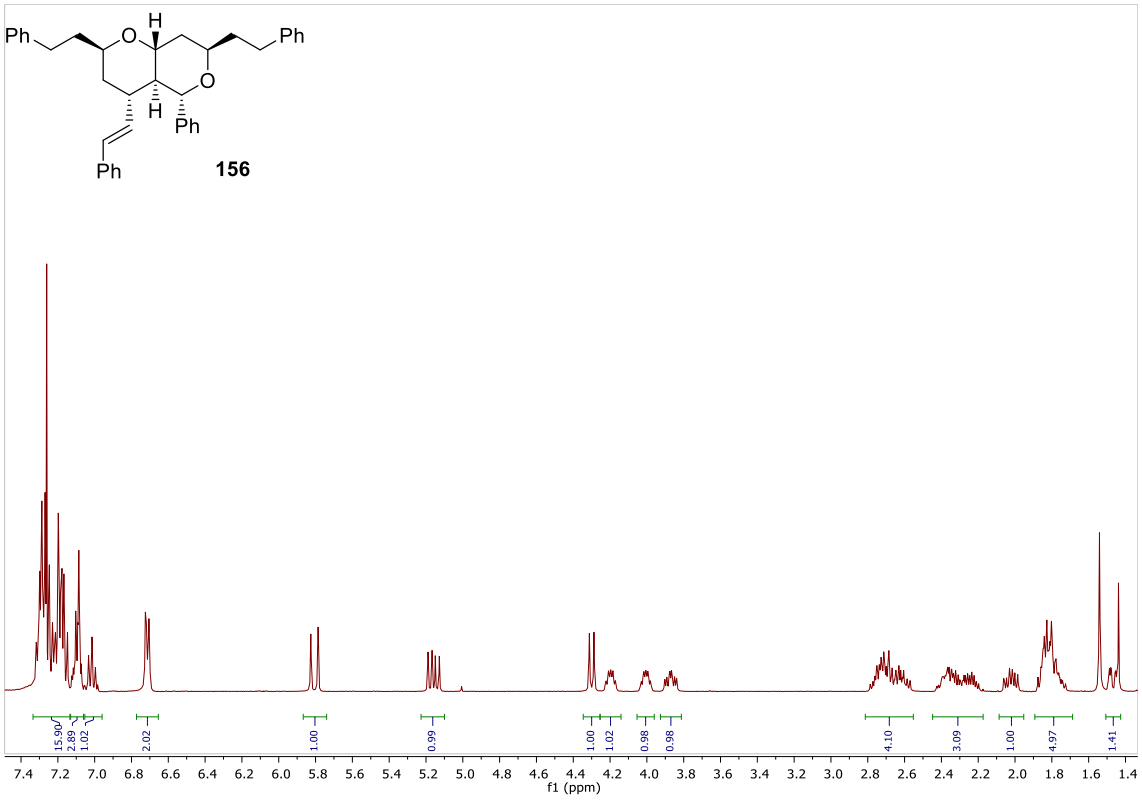

142.03
136.74
132.01
130.27
128.76
128.62
128.54
127.87
126.64
126.07
70.84
69.08
42.84
39.40
32.27
f1 (ppm)

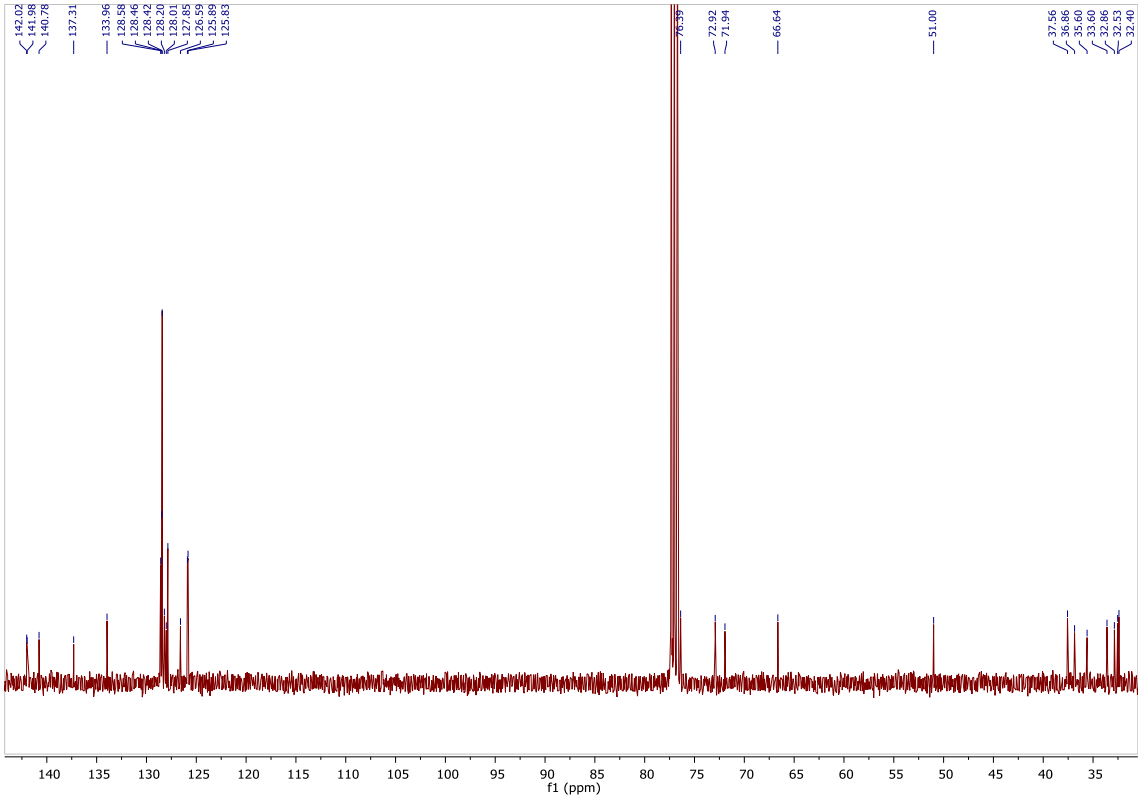

Ph
O
H
Ph
O
H
Ph
Ph
154
5.84
6.63
3.12
0.97
2.01
0.99
1.00
1.00
1.06
1.00
1.01
4.22
2.00
1.01
1.05
4.40
1.25
1.48
f1 (ppm)

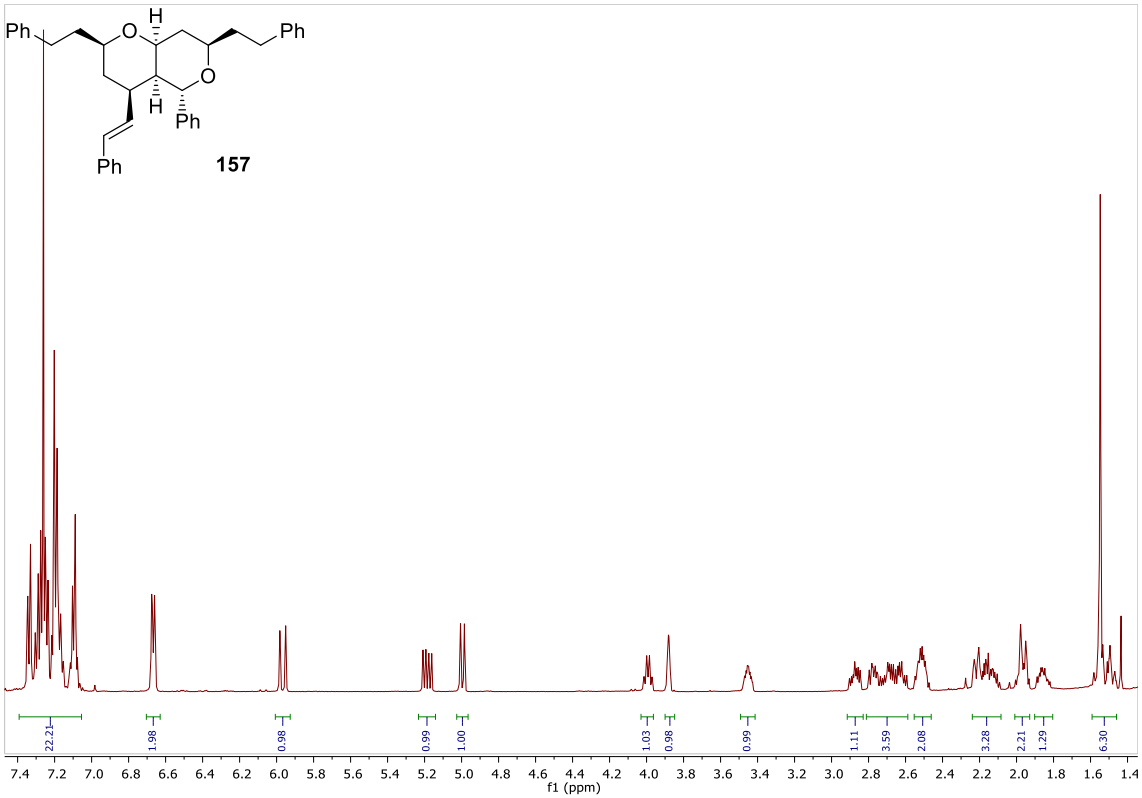

142.10
140.90
137.35
134.02
128.56
128.47
128.41
128.34
128.14
128.01
127.84
126.55
125.87
125.80
125.76
76.86
75.96
75.15
72.95
50.62
42.40
40.09
37.67
35.35
33.43
32.51
31.63
f1 (ppm)

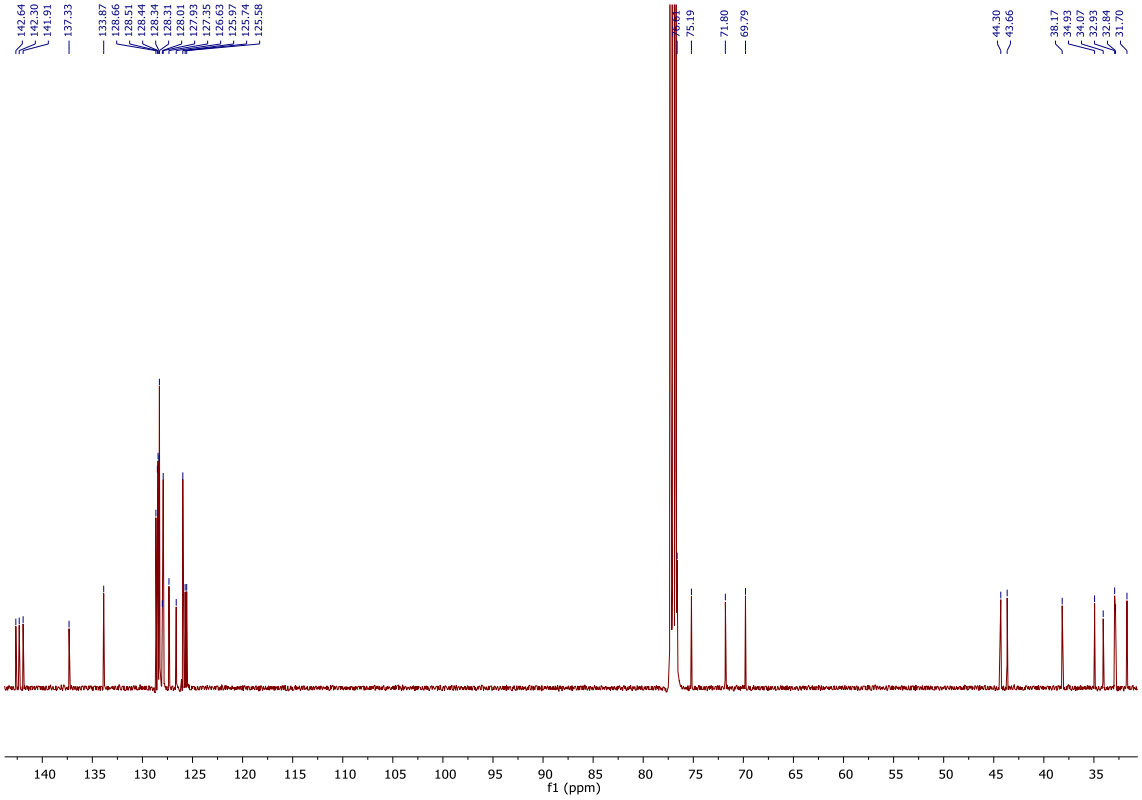

Ph
O
H
Ph
O
H
Ph
Ph
155
21.30
6.07
0.97
0.98
1.00
2.02
1.00
4.06
3.13
1.06
2.11
3.23
1.14
f1 (ppm)

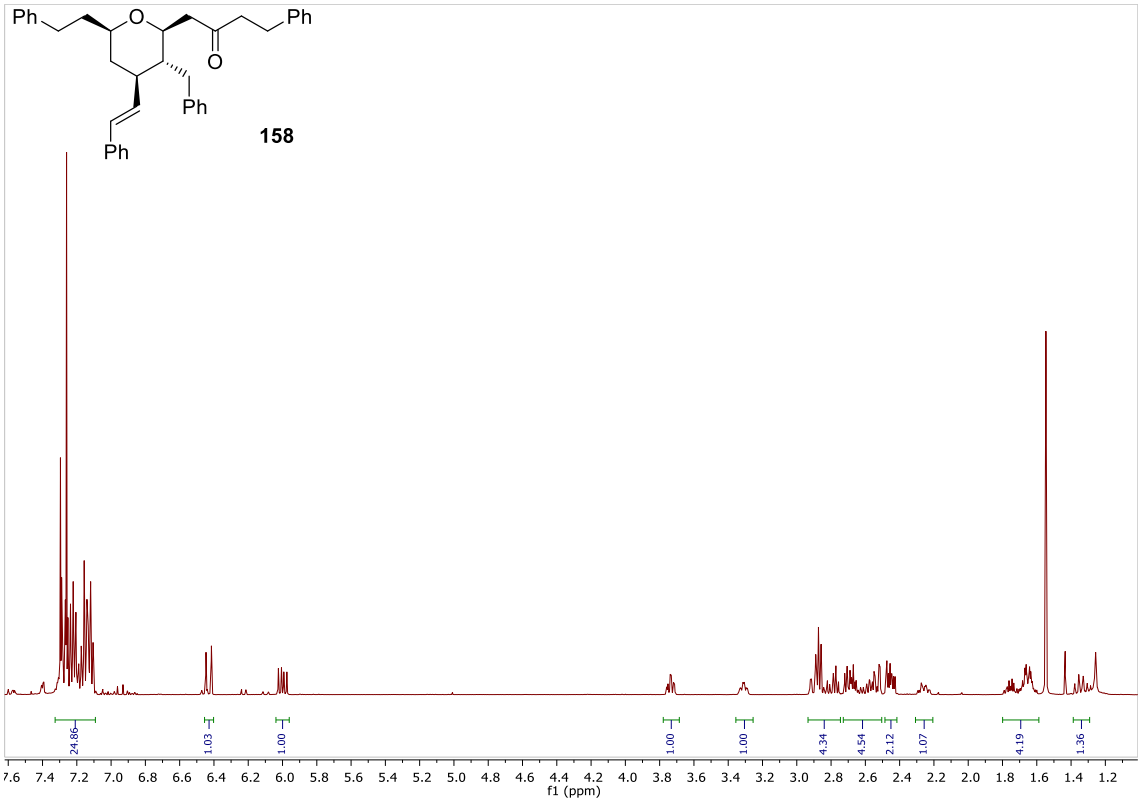

141.89
139.05
137.33
132.57
129.93
128.69
128.49
128.44
128.36
128.31
128.15
128.06
127.43
126.15
125.89
125.80
73.89
73.24
71.61
62.61
48.74
36.14
35.77
35.52
33.42
32.86
32.45
f1 (ppm)

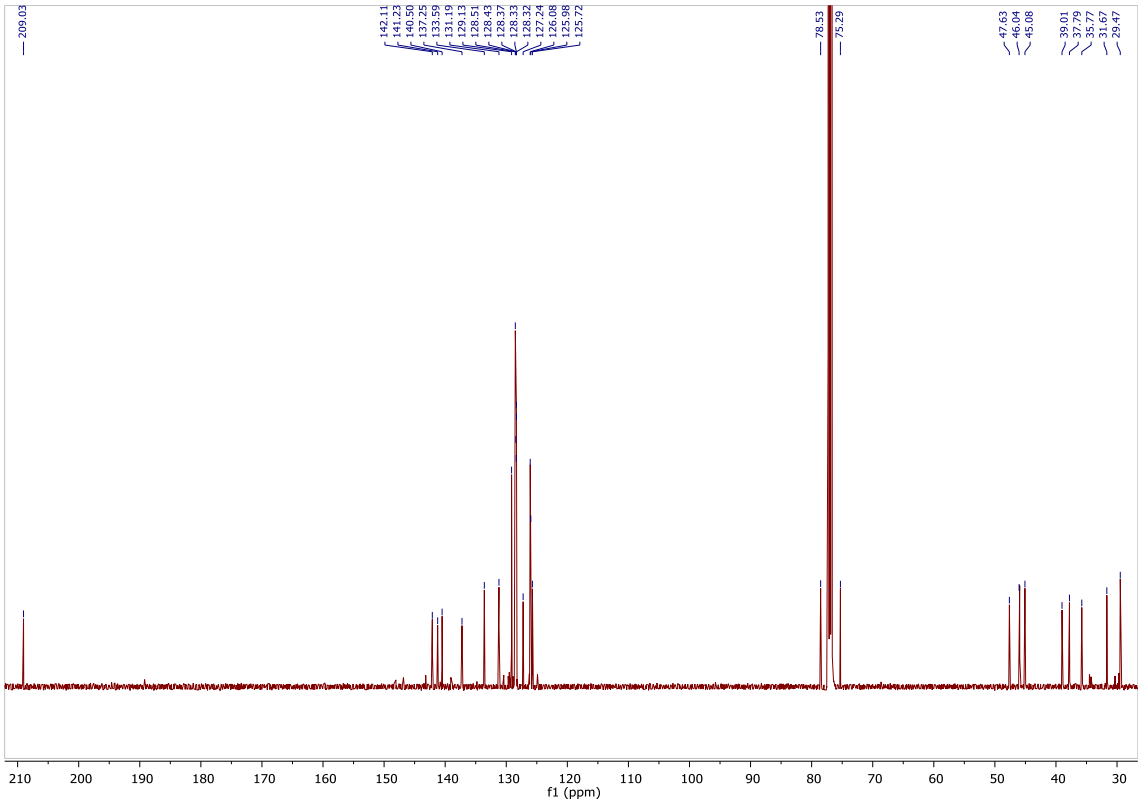

Ph
O
H
Ph
O
H
Ph
Ph
156
15.90
2.89
1.02
2.02
1.00
0.99
1.00
1.02
0.98
0.98
4.10
3.09
1.00
4.97
1.41
f1 (ppm)

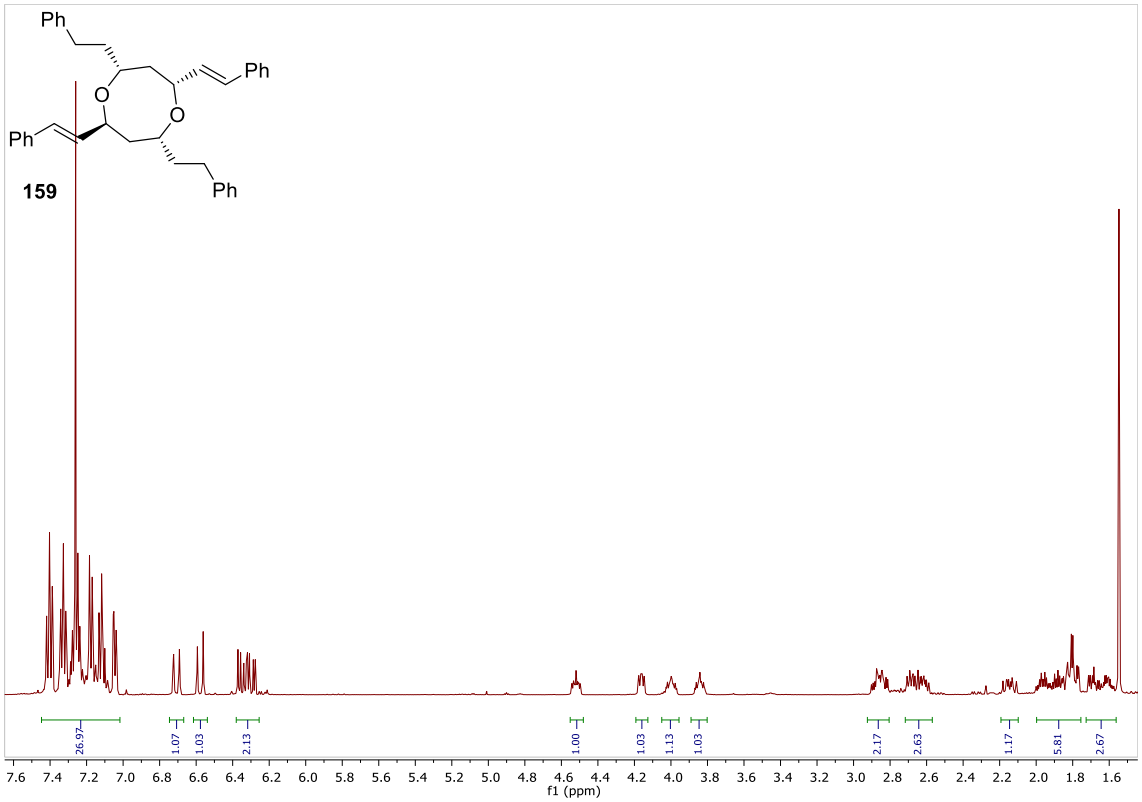

142.02
141.98
140.78
137.31
133.96
128.58
128.46
128.42
128.20
128.01
127.85
126.59
125.89
125.83
76.39
72.92
71.94
66.64
51.00
37.56
36.86
35.60
33.60
32.86
32.53
32.40
f1 (ppm)

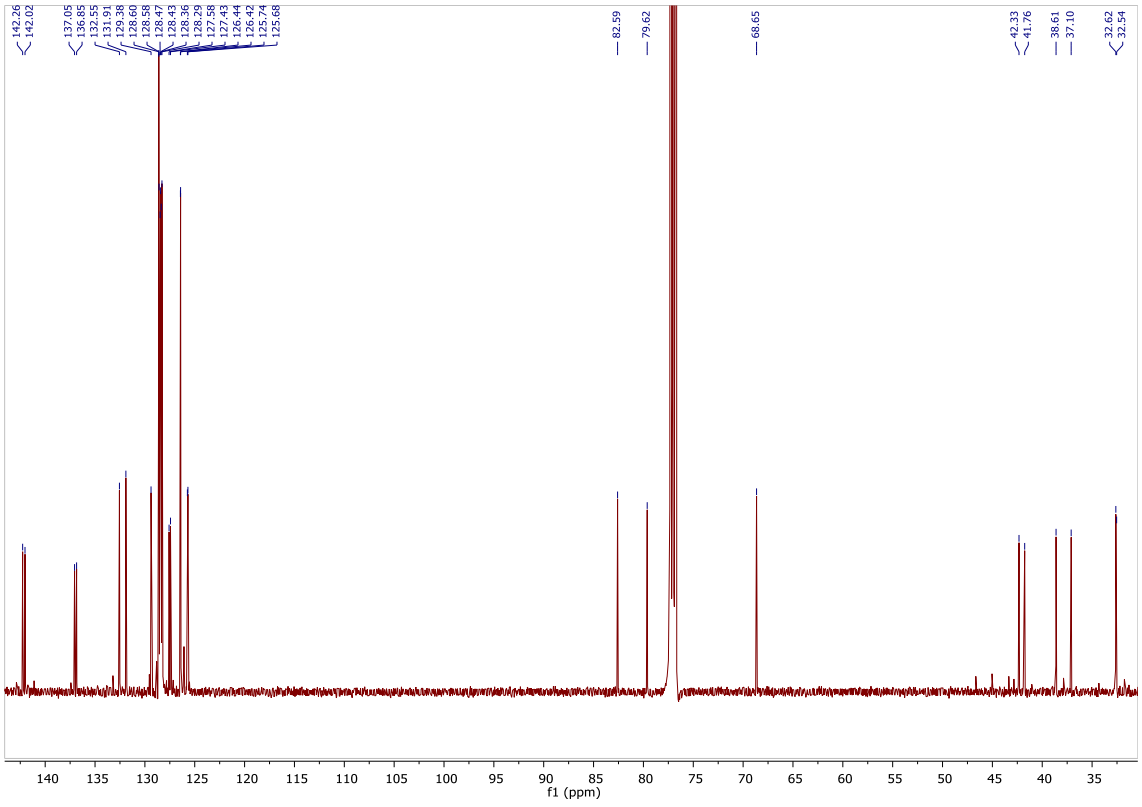

Ph
O
H
Ph
O
H
Ph
Ph
157
22.21
1.98
0.98
0.99
1.00
1.03
0.98
0.99
1.11
3.59
2.08
3.28
2.21
1.29
6.30
f1 (ppm)

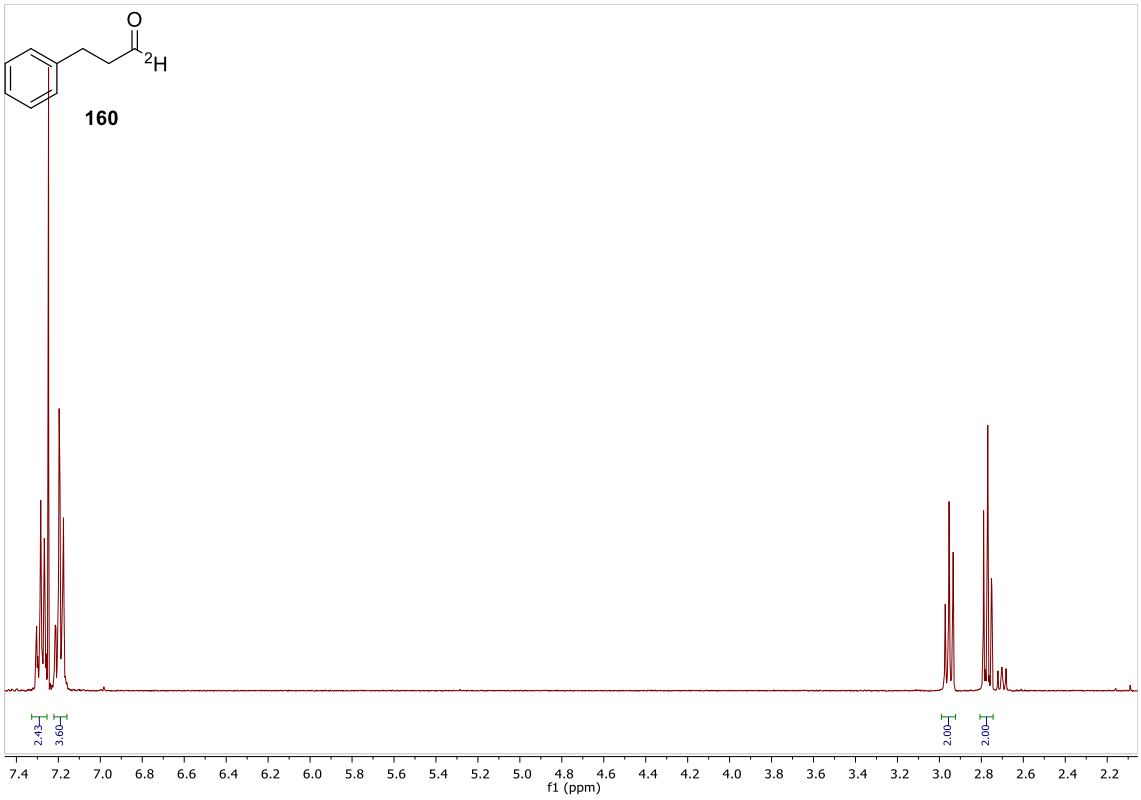

142.64
142.30
141.91
137.33
133.87
128.66
128.51
128.44
128.34
128.31
128.01
127.93
127.35
126.63
125.97
125.74
125.58
76.83
75.19
71.80
69.79
44.30
43.66
38.17
34.93
34.07
32.93
32.84
31.70
f1 (ppm)

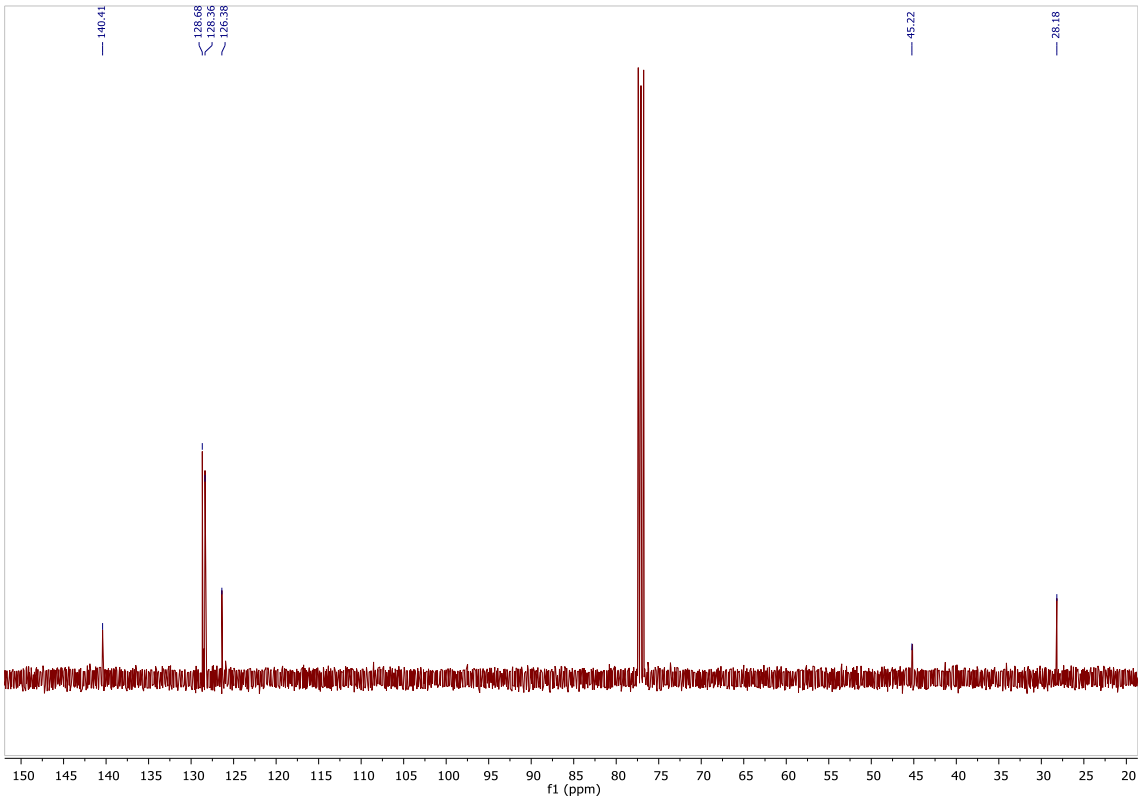

Ph
O
Ph
O
Ph
Ph
158
24.86
1.03
1.00
1.00
1.00
4.34
4.54
2.12
1.07
4.19
1.36
f1 (ppm)

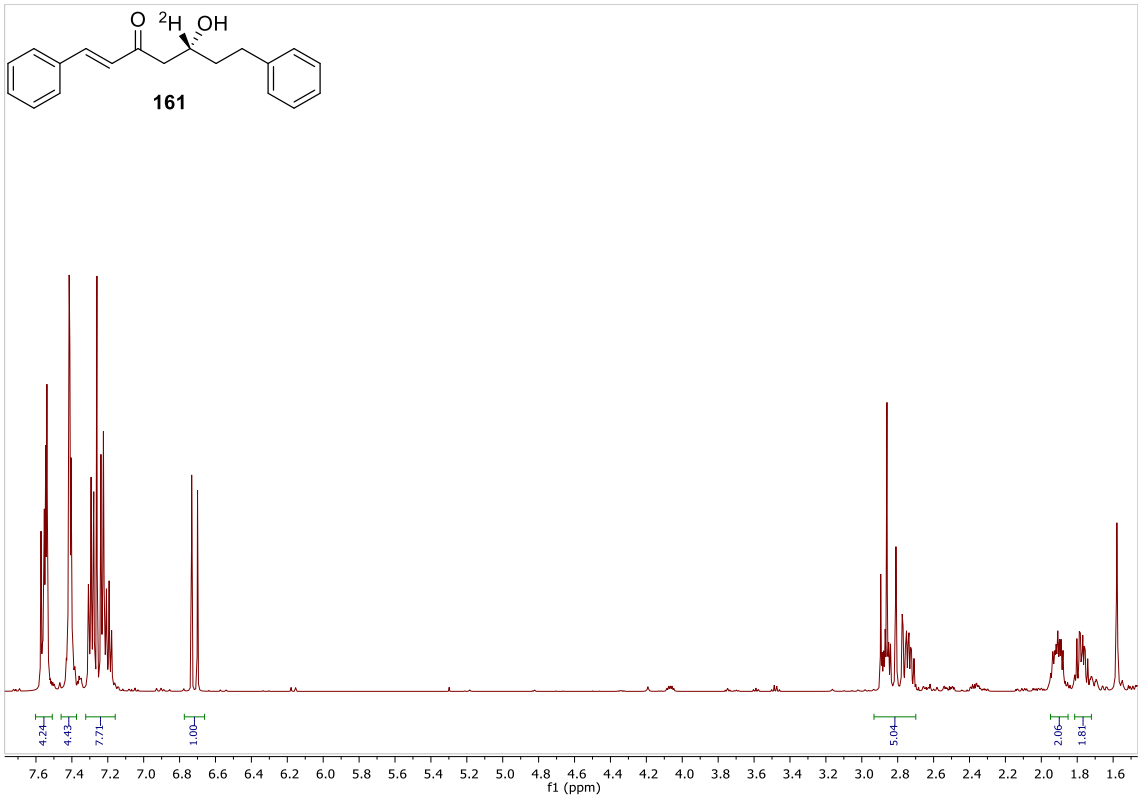

209.03
142.11
141.23
140.50
137.25
133.59
131.19
129.13
128.51
128.43
128.37
128.33
128.32
127.24
126.08
125.98
125.72
78.53
75.29
47.63
46.04
45.08
39.01
37.79
35.77
31.67
29.47
f1 (ppm)

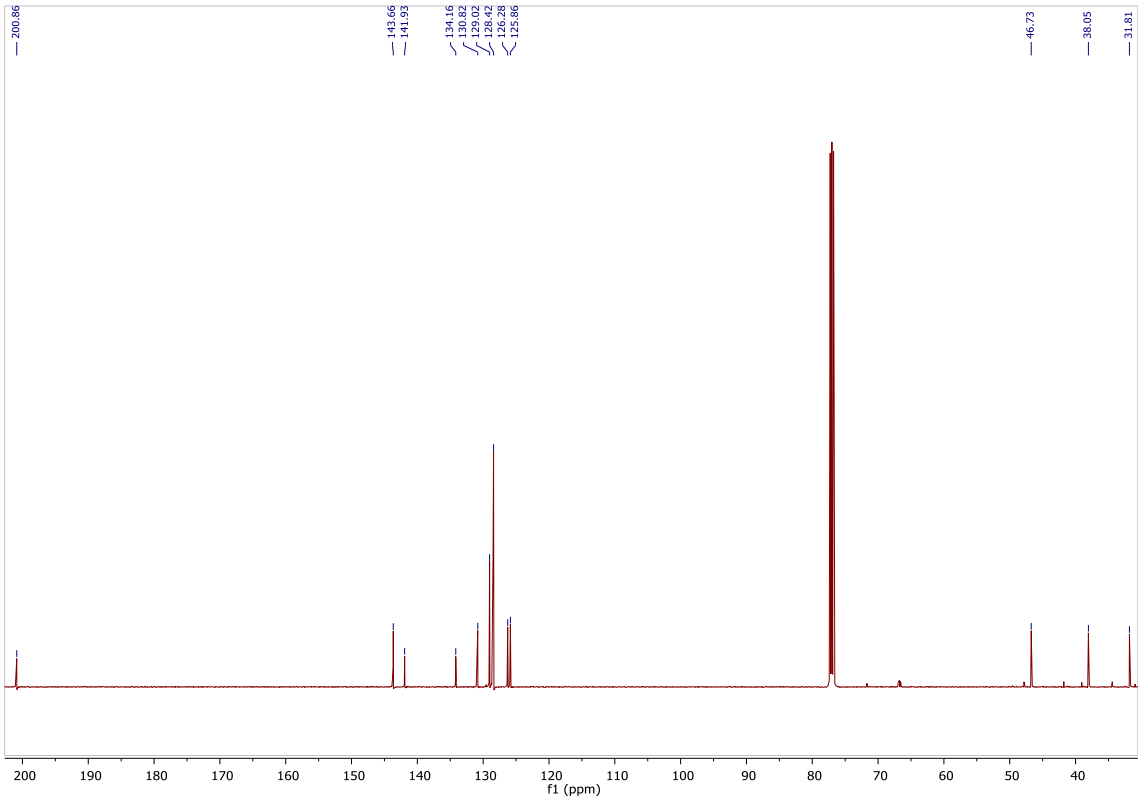

Ph
Ph
Ph
Ph
O
O
159
26.97
1.07
1.03
2.13
1.00
1.03
1.13
1.03
2.17
2.63
1.17
5.81
2.67
f1 (ppm)

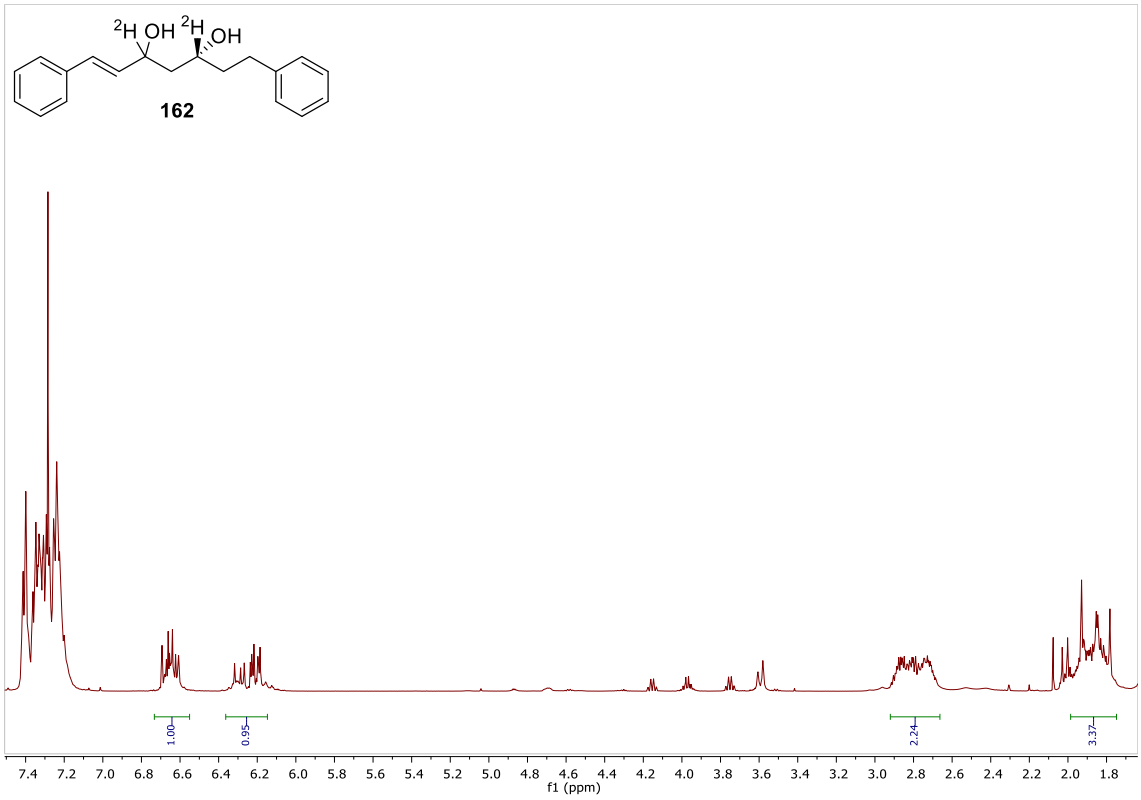

142.26
142.02
137.05
136.65
132.55
131.91
129.38
128.60
128.58
128.47
128.43
128.36
128.29
127.58
127.43
126.44
126.42
125.74
125.68
82.59
79.62
68.65
42.33
41.76
38.61
37.10
32.62
32.54
f1 (ppm)

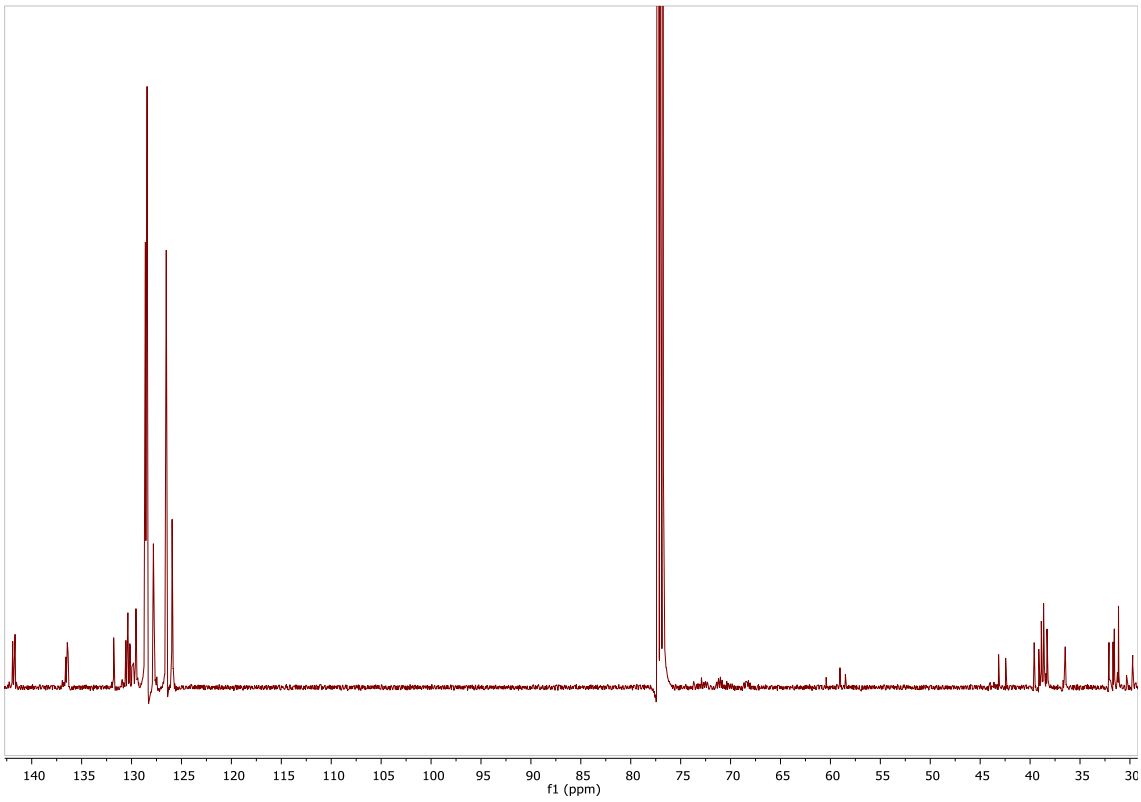

O
2H
160
2.43
3.60
2.00
2.00
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2
f1 (ppm)

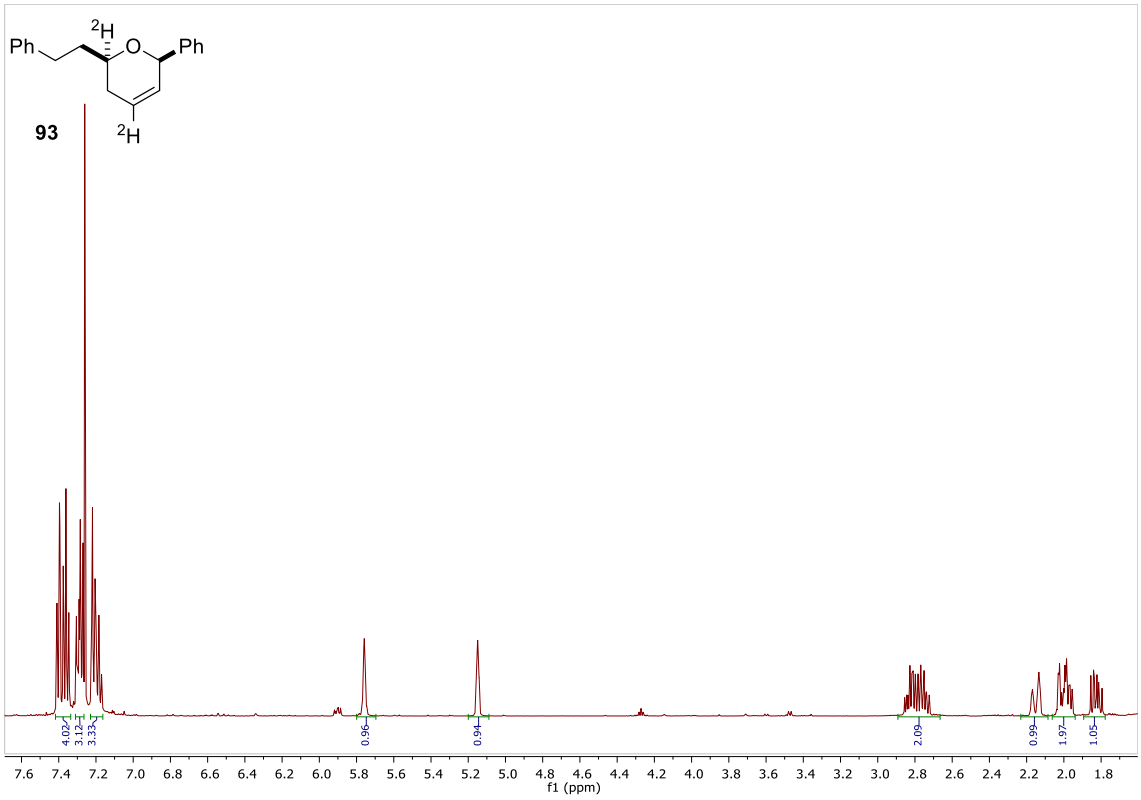

140.41
128.68
128.36
126.38
45.22
28.18
150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)

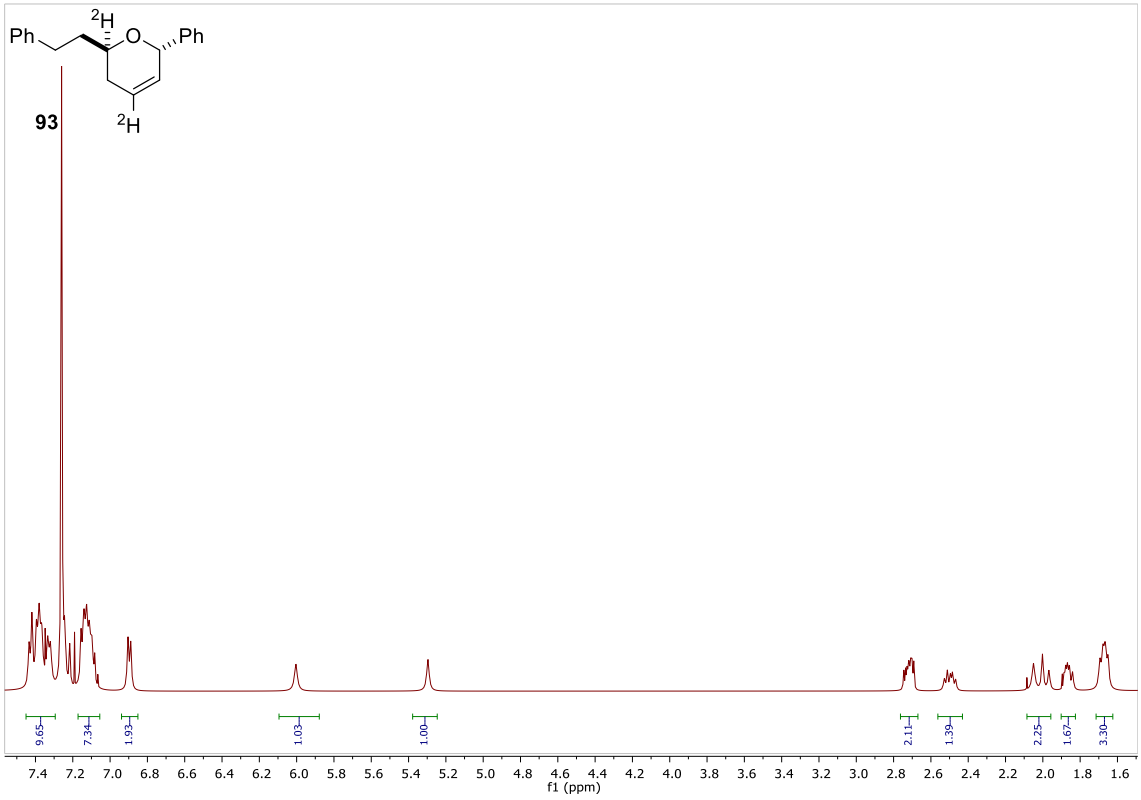

O
2H
OH
161
4.24
4.43
7.71
1.00
5.04
2.05
1.81
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)

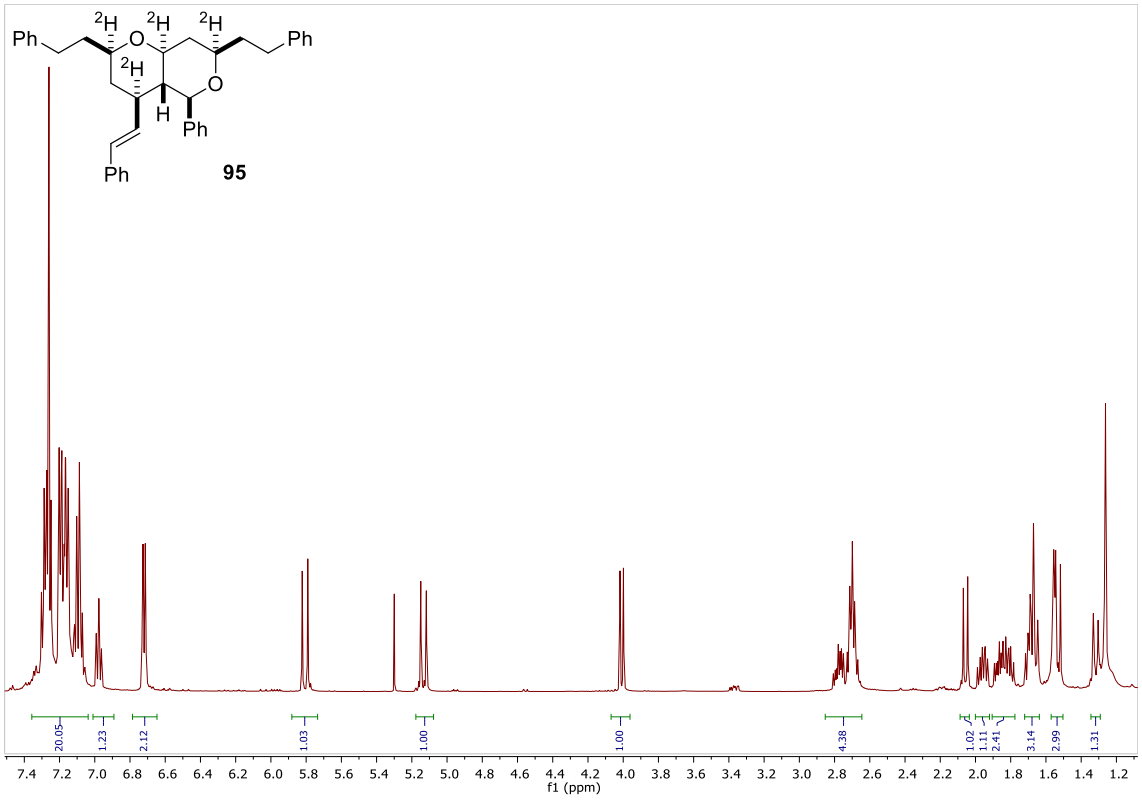

200.86
143.66
141.93
134.16
130.82
129.02
128.42
126.28
125.86
46.73
38.05
31.81
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40
f1 (ppm)

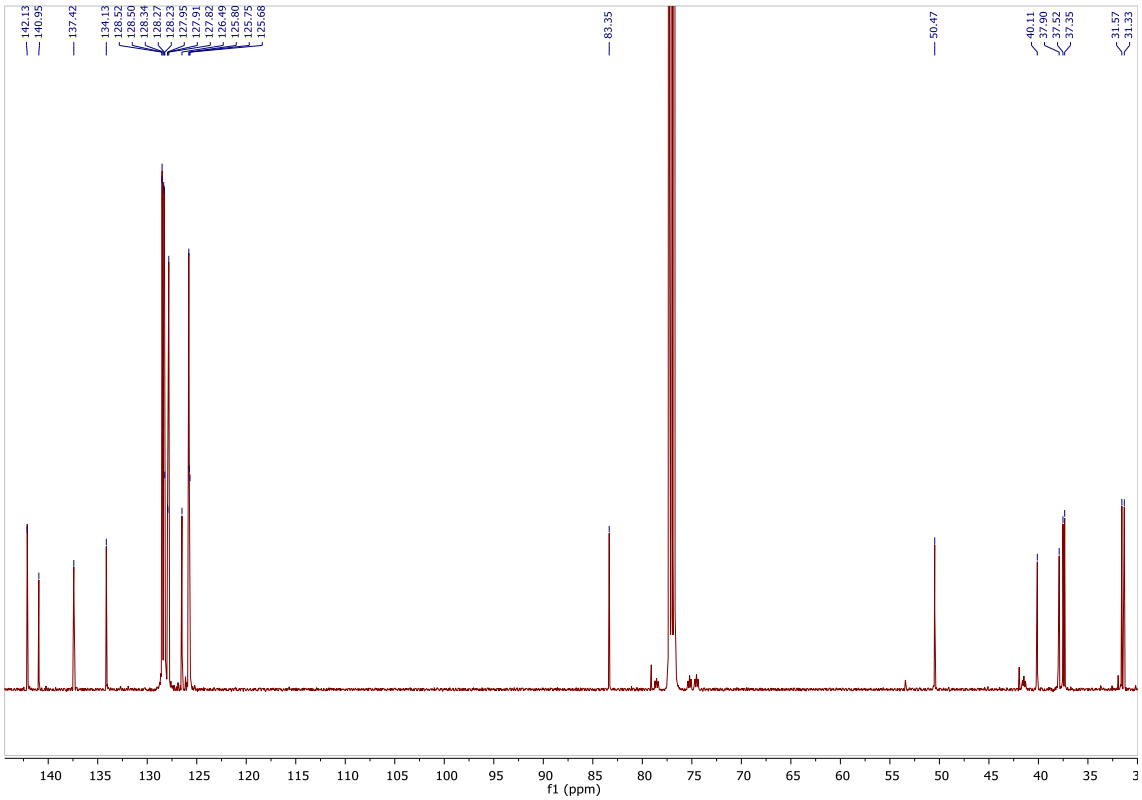

^{2}H OH ^{2}H OH
162
1.00
0.95
2.24
3.37
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8
f1 (ppm)

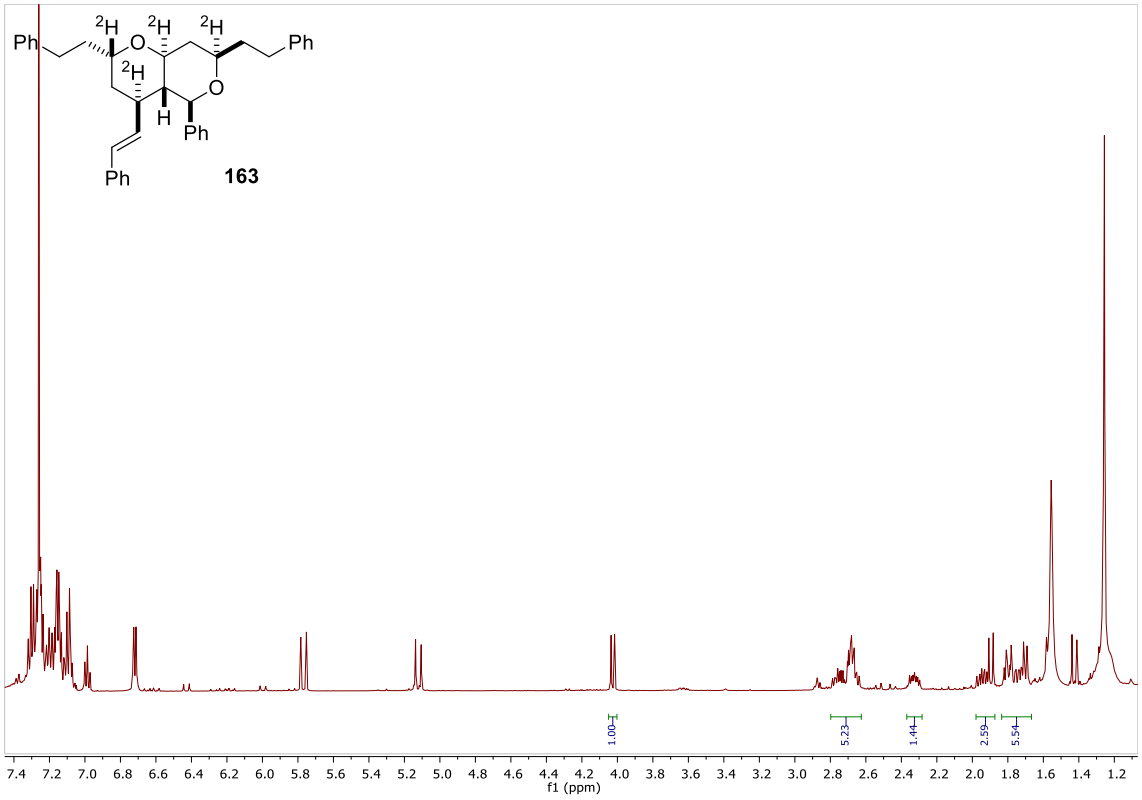

140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30
f1 (ppm)

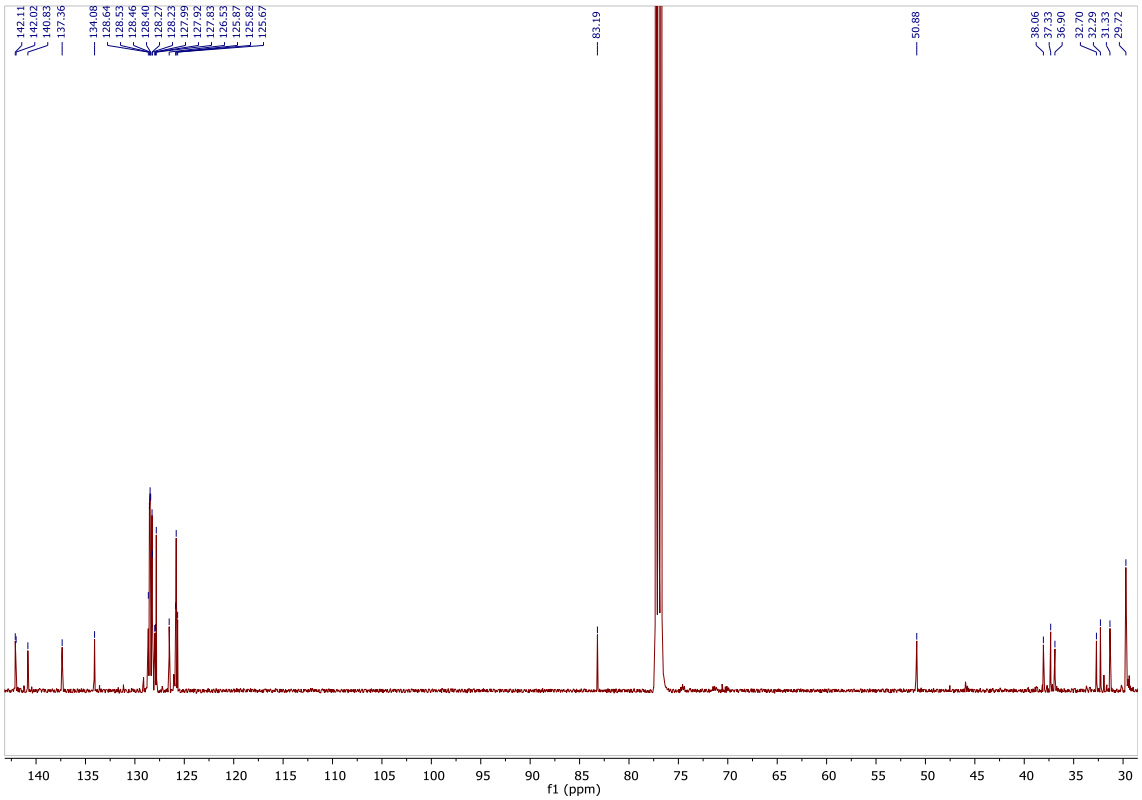

Ph
^{2}H
O
Ph
^{2}H
93
4.02
3.12
3.33
0.96
0.94
2.09
0.99
1.97
1.05
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8
f1 (ppm)

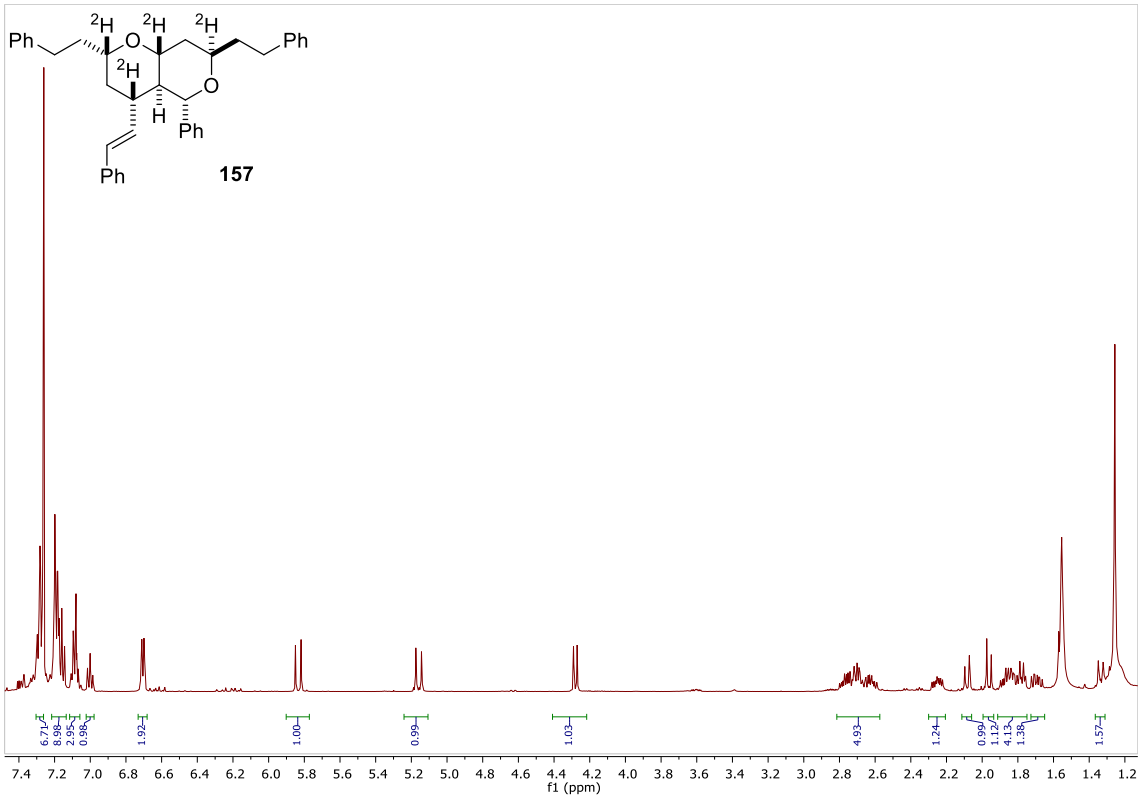

Ph
^{2}H
O
Ph
^{2}H
93
9.65
7.34
1.93
1.03
1.00
2.11
1.39
2.25
1.67
3.30
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)

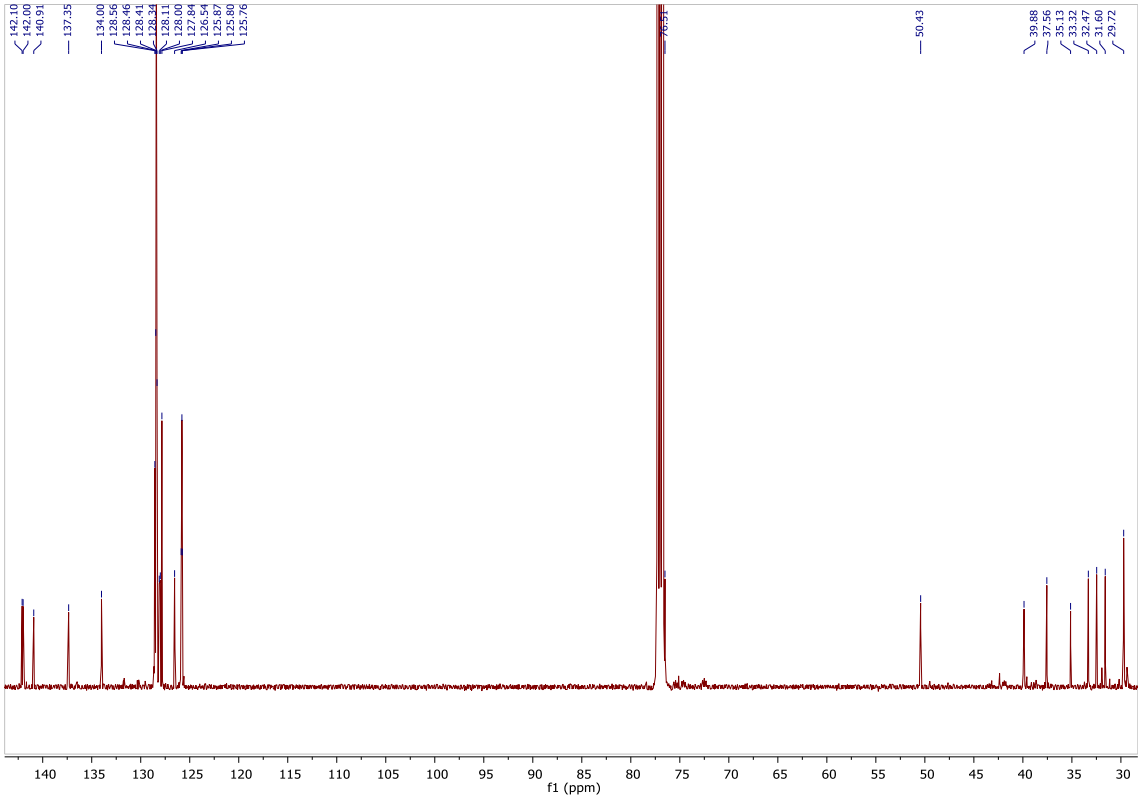

Ph
^{2}H
O
^{2}H
^{2}H
Ph
^{2}H
O
H
Ph
Ph
95
20.05
1.23
2.12
1.03
1.00
1.00
4.38
1.02
1.11
2.41
3.14
2.99
1.31
f1 (ppm)

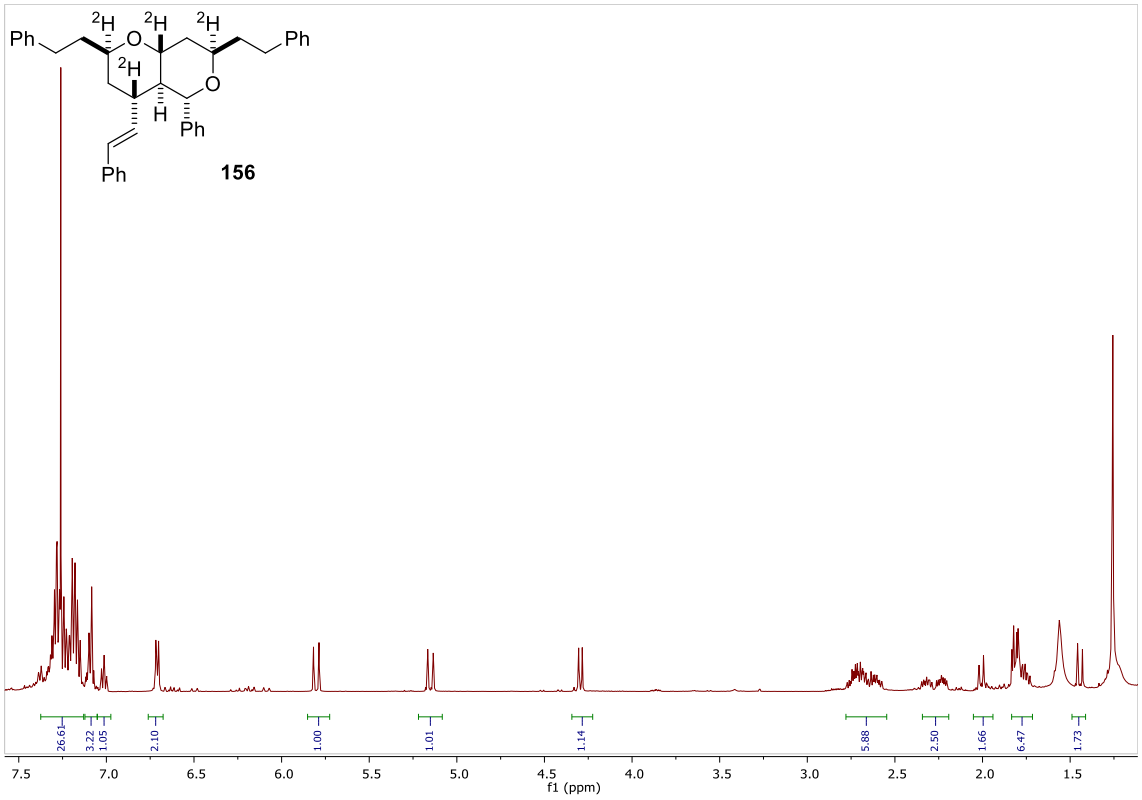

142.13
140.95
137.42
134.13
128.52
128.50
128.34
128.27
128.23
127.95
127.91
127.82
126.49
125.80
125.75
125.68
83.35
50.47
40.11
37.90
37.52
37.35
31.57
31.33
f1 (ppm)

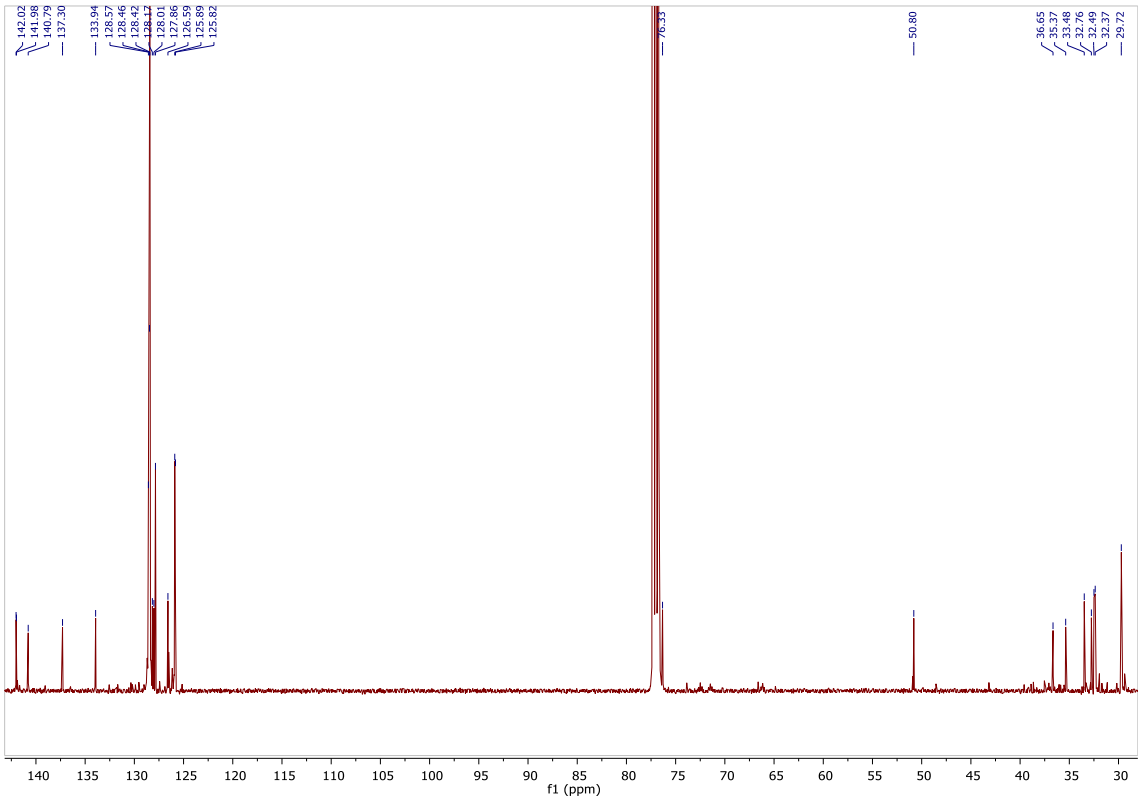

Ph
^{2}H
^{2}H
^{2}H
O
^{2}H
H
O
Ph
Ph
Ph
163
1.00
5.23
1.44
2.59
5.54
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)

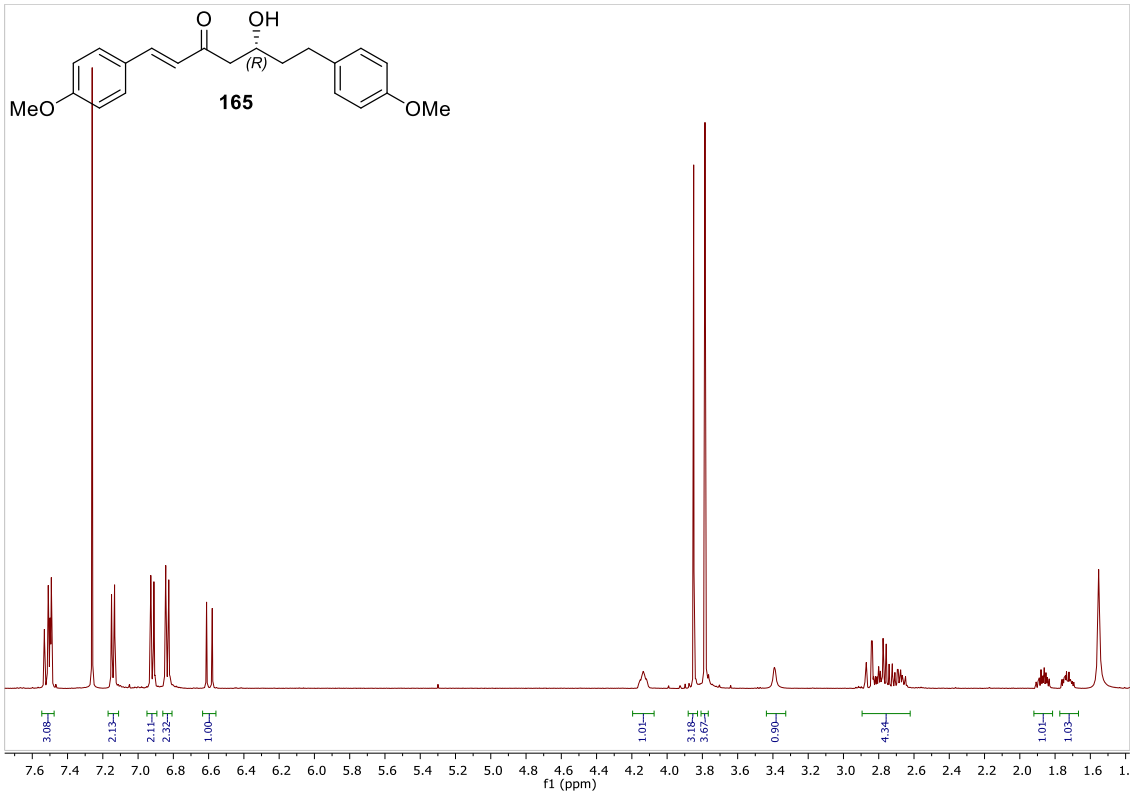

142.11
142.02
140.83
137.36
134.08
128.64
128.53
128.46
128.40
128.27
128.23
127.99
127.92
127.83
126.53
125.87
125.82
125.67
83.19
50.88
38.06
37.33
36.90
32.70
32.29
31.33
29.72
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30
f1 (ppm)

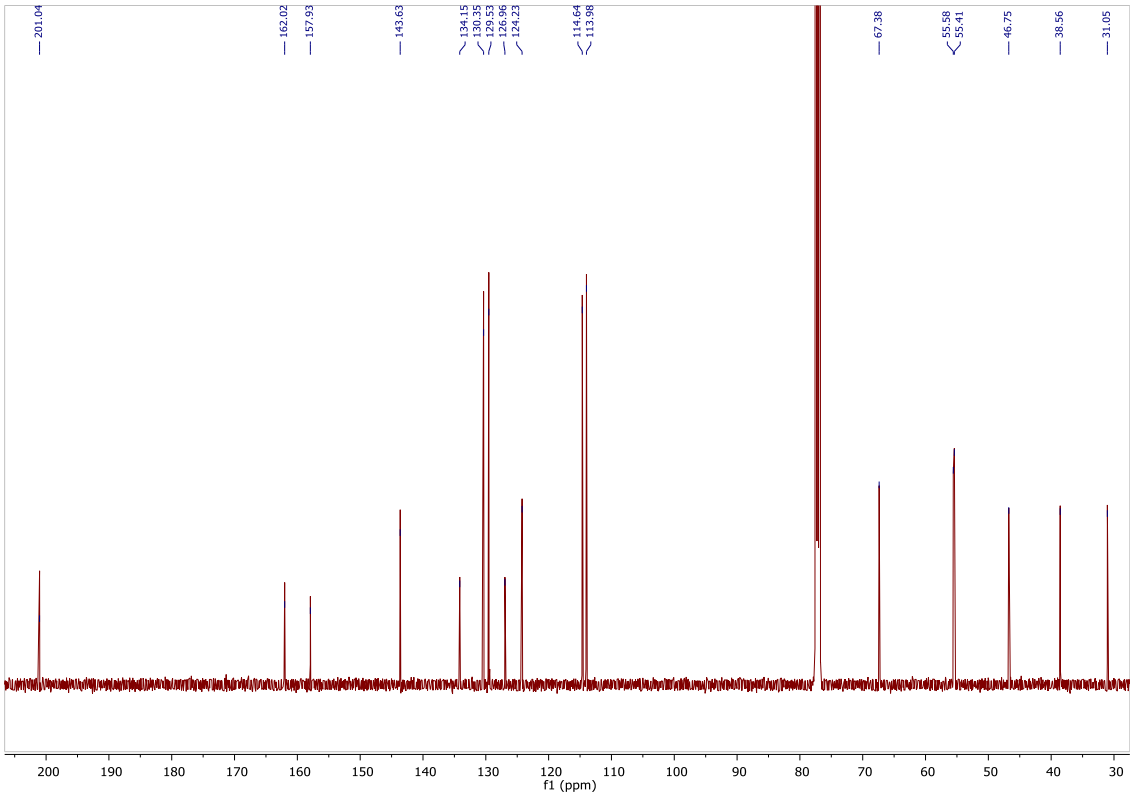

Ph
^{2}H
^{2}H
^{2}H
Ph
O
^{2}H
O
H
Ph
Ph
157
6.71
8.98
2.95
0.98
1.92
1.00
0.99
1.03
4.93
1.24
0.99
1.12
4.13
1.38
1.57
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)

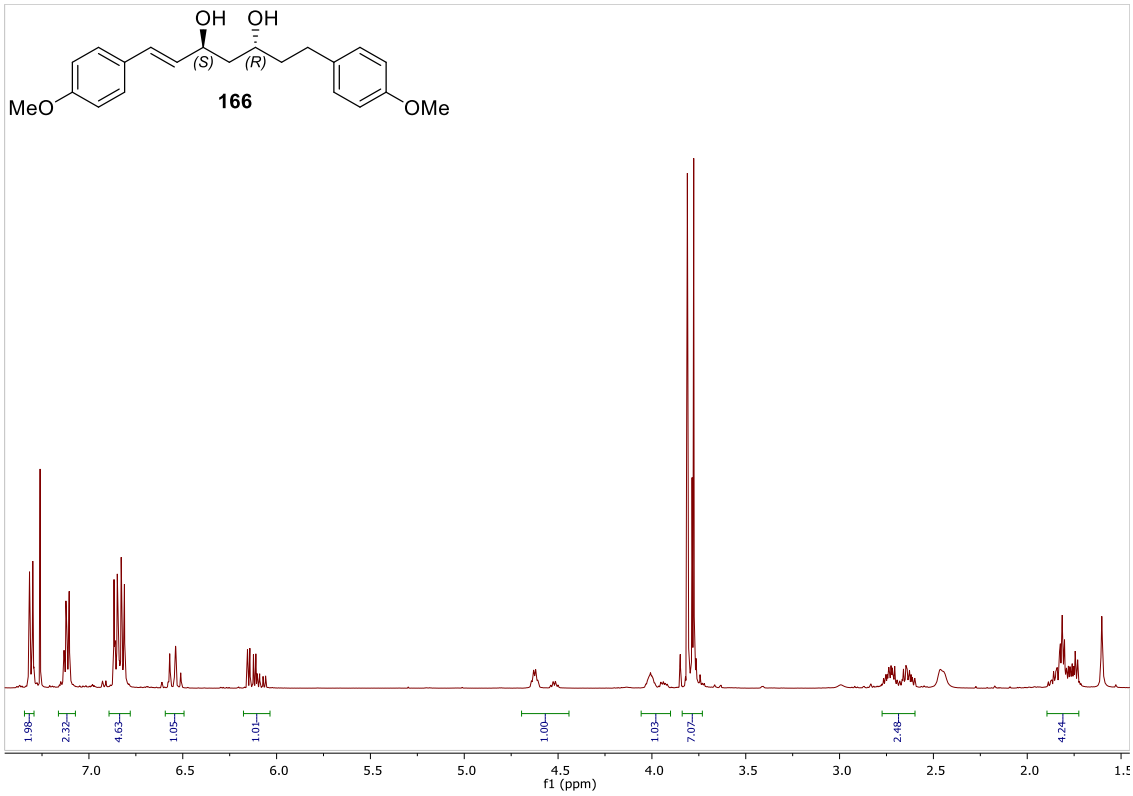

142.10
142.00
140.91
137.35
134.00
128.56
128.46
128.41
128.24
128.11
129.00
127.94
126.54
125.87
125.80
125.76
76.51
50.43
39.88
37.56
35.13
33.32
32.47
31.60
29.72
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30
f1 (ppm)

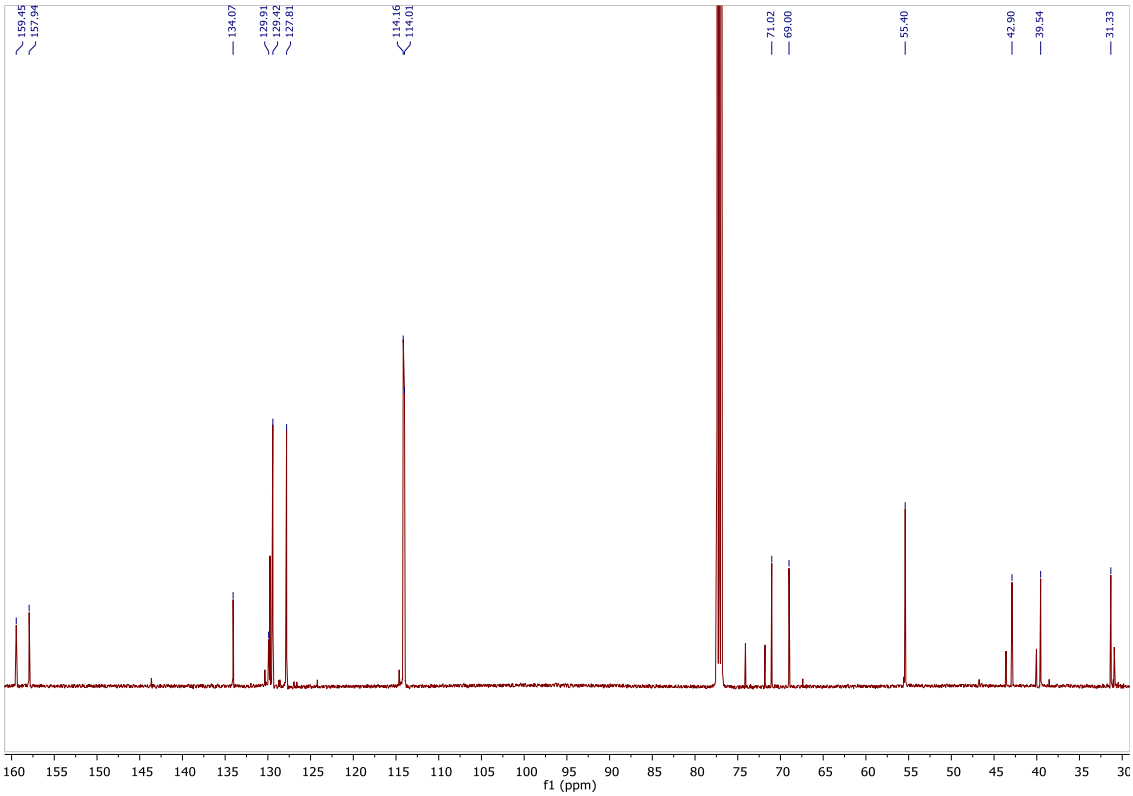

Ph
2H
O
2H
2H
2H
O
H
Ph
Ph
Ph
156
26.61
3.22
1.05
2.10
1.00
1.01
1.14
5.88
2.50
1.66
6.47
1.73
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

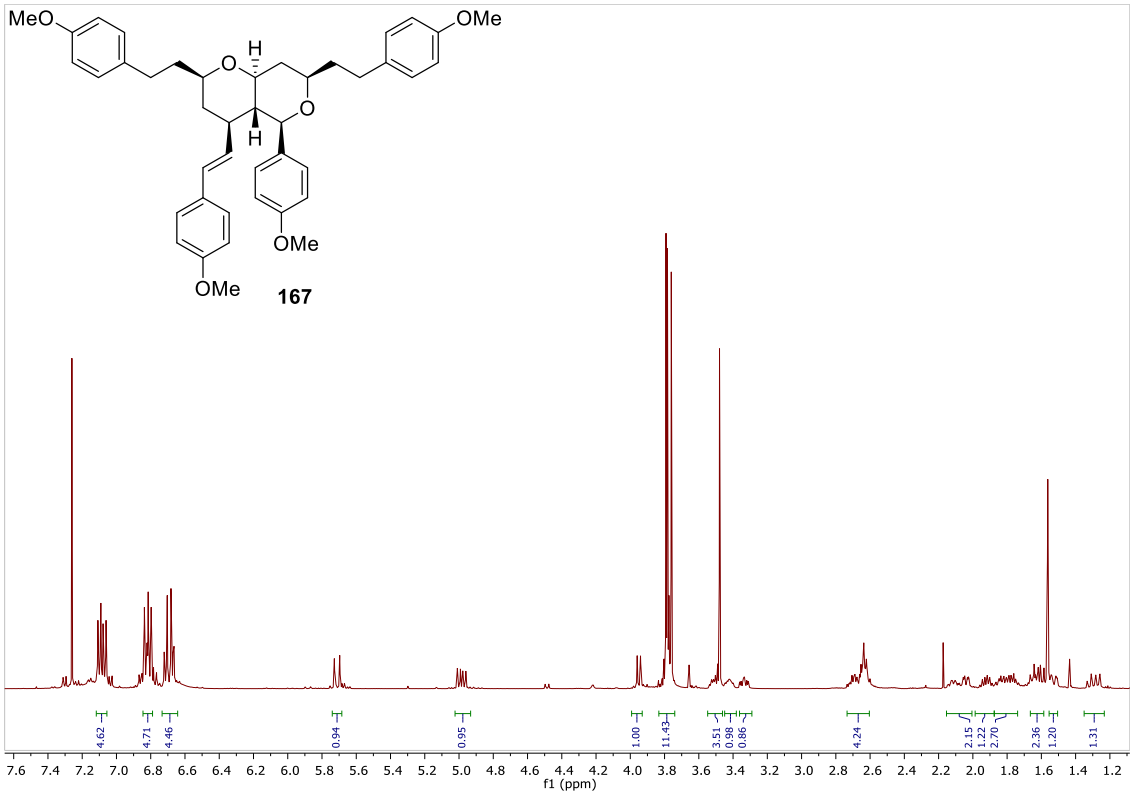

142.02
141.98
140.79
137.30
133.94
128.57
128.46
128.42
128.17
128.01
127.86
126.59
125.89
125.82
76.33
50.80
36.65
35.37
33.48
32.76
32.49
32.37
29.72
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
f1 (ppm)

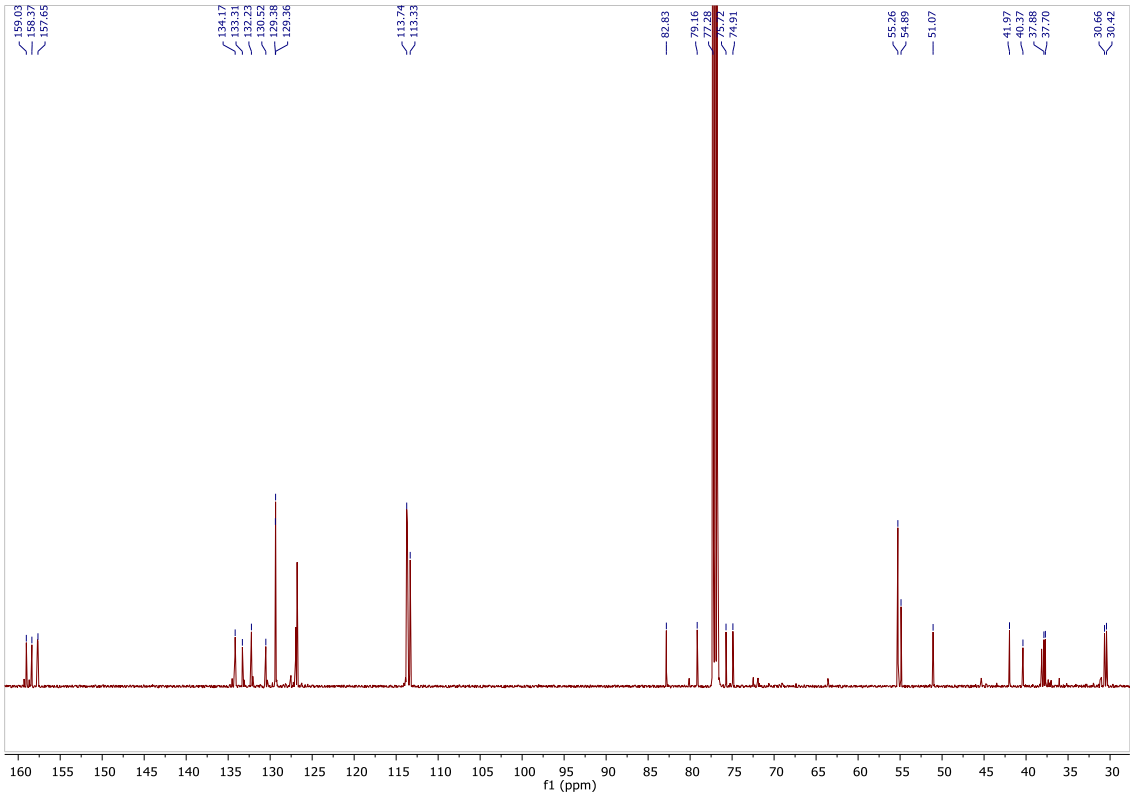

O
OH
(R)
MeO
OMe
165
3.08
2.13
2.11
2.32
1.00
1.01
3.18
3.67
0.90
4.34
1.01
1.03
f1 (ppm)

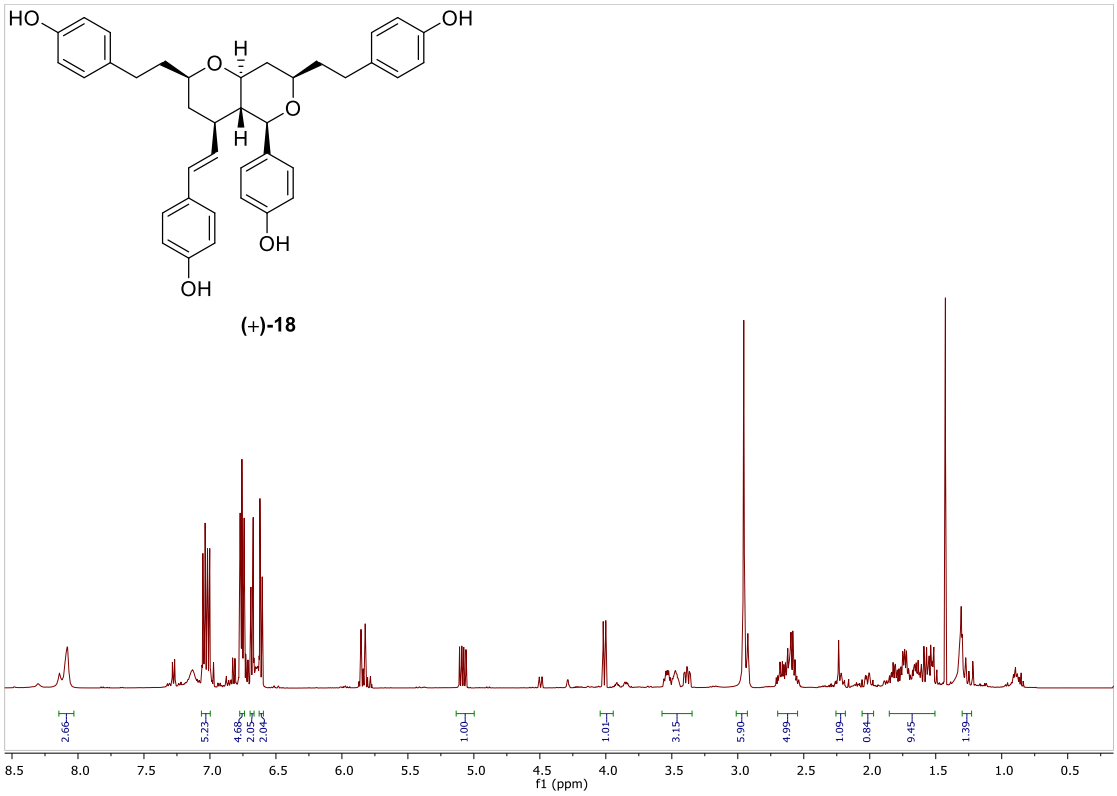

201.04
162.02
157.93
143.63
134.15
130.35
129.53
126.96
124.23
114.64
113.98
67.38
55.58
55.41
46.75
38.56
31.05
f1 (ppm)


OH
OH
(S)
(R)
MeO
OMe
166
1.98
2.32
4.63
1.05
1.01
1.00
1.03
7.07
2.48
4.24
f1 (ppm)

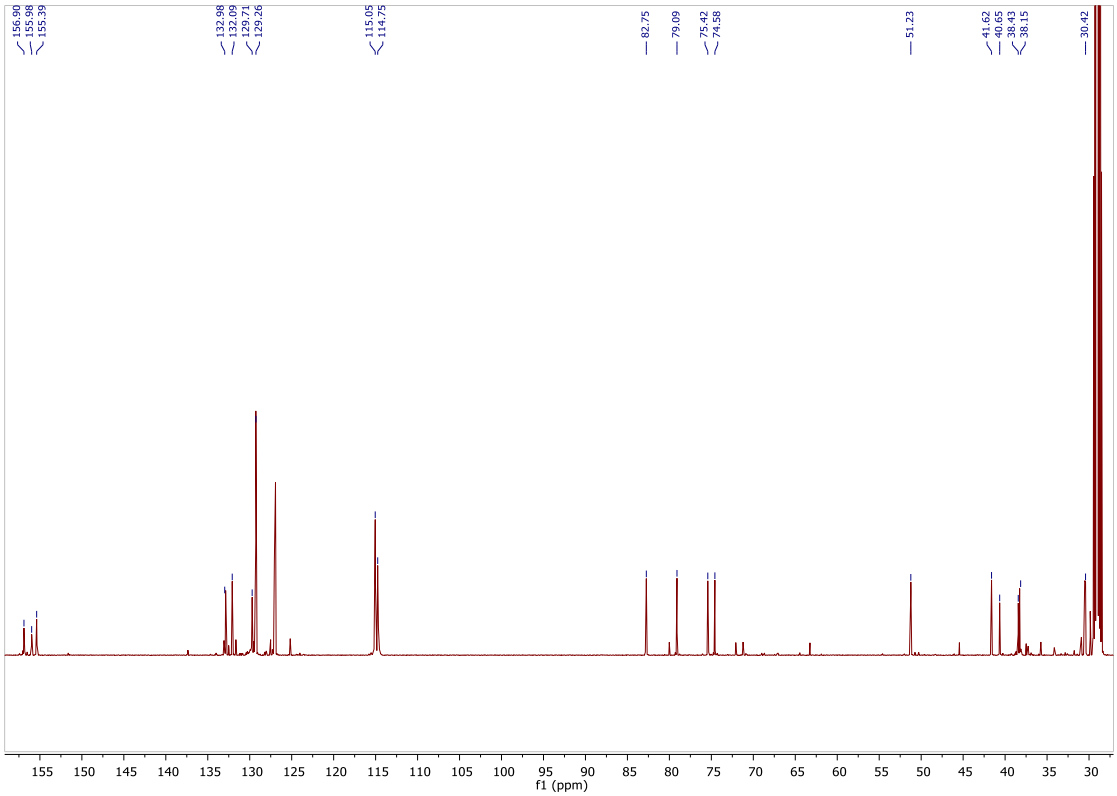

159.45
157.94
134.07
129.91
129.42
127.81
114.16
114.01
71.02
69.00
55.40
42.90
39.54
31.33
f1 (ppm)

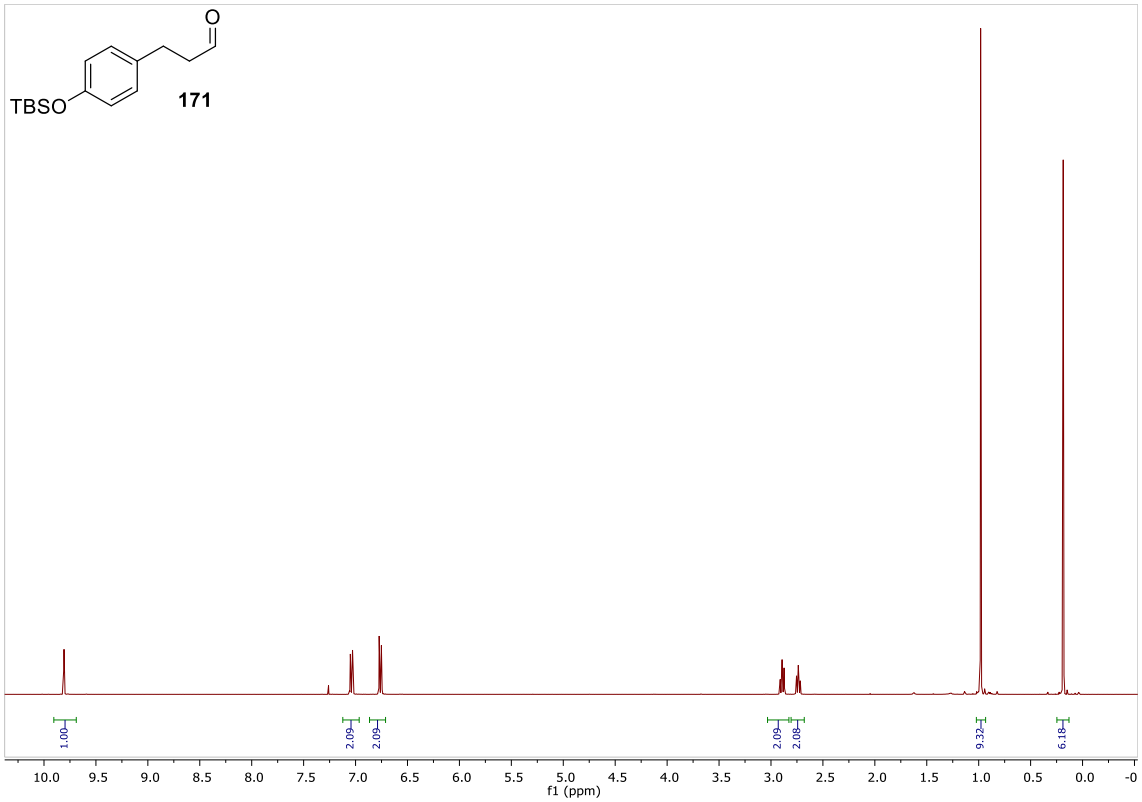

MeO
OMe
H
O
O
H
OMe
OMe
167
4.62
4.71
4.46
0.94
0.95
1.00
11.43
3.51
0.98
0.86
4.24
2.15
1.22
2.70
2.36
1.20
1.31
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)

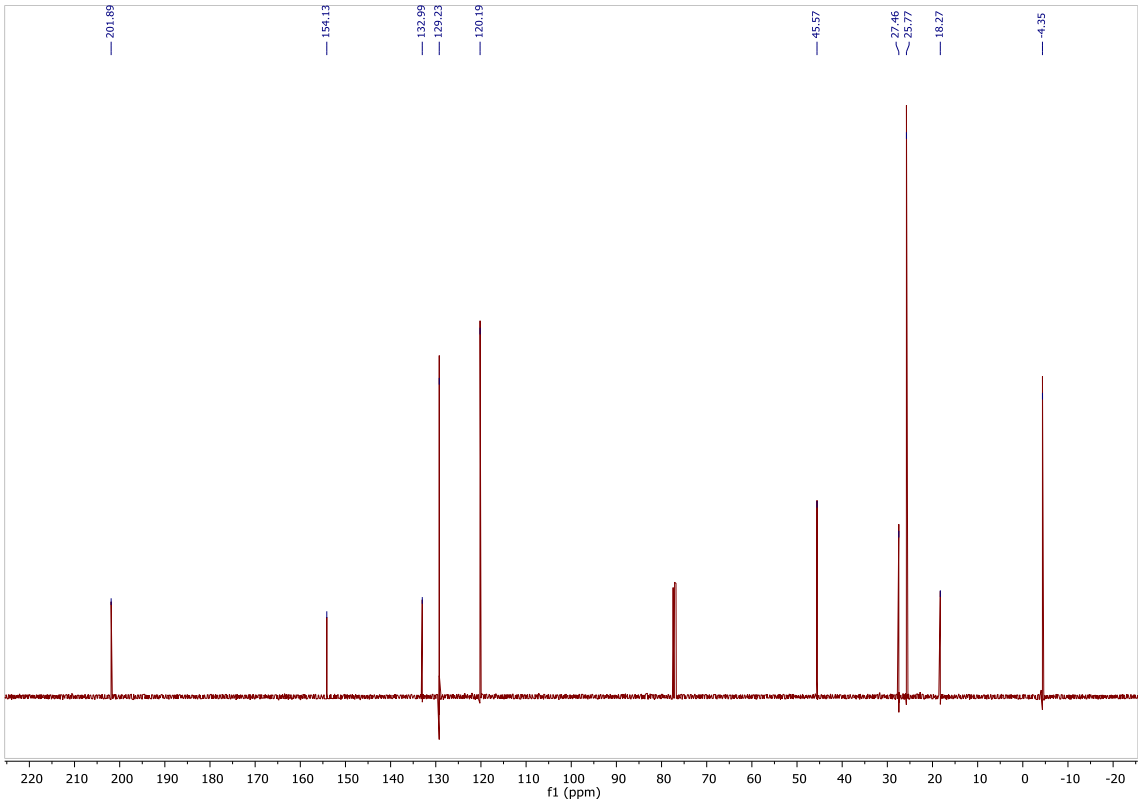

159.03
158.37
157.65
134.17
133.31
133.23
130.52
129.38
129.36
113.74
113.33
82.83
79.16
77.28
75.72
74.91
55.26
54.89
51.07
41.97
40.37
37.88
37.70
30.66
30.42
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30
f1 (ppm)

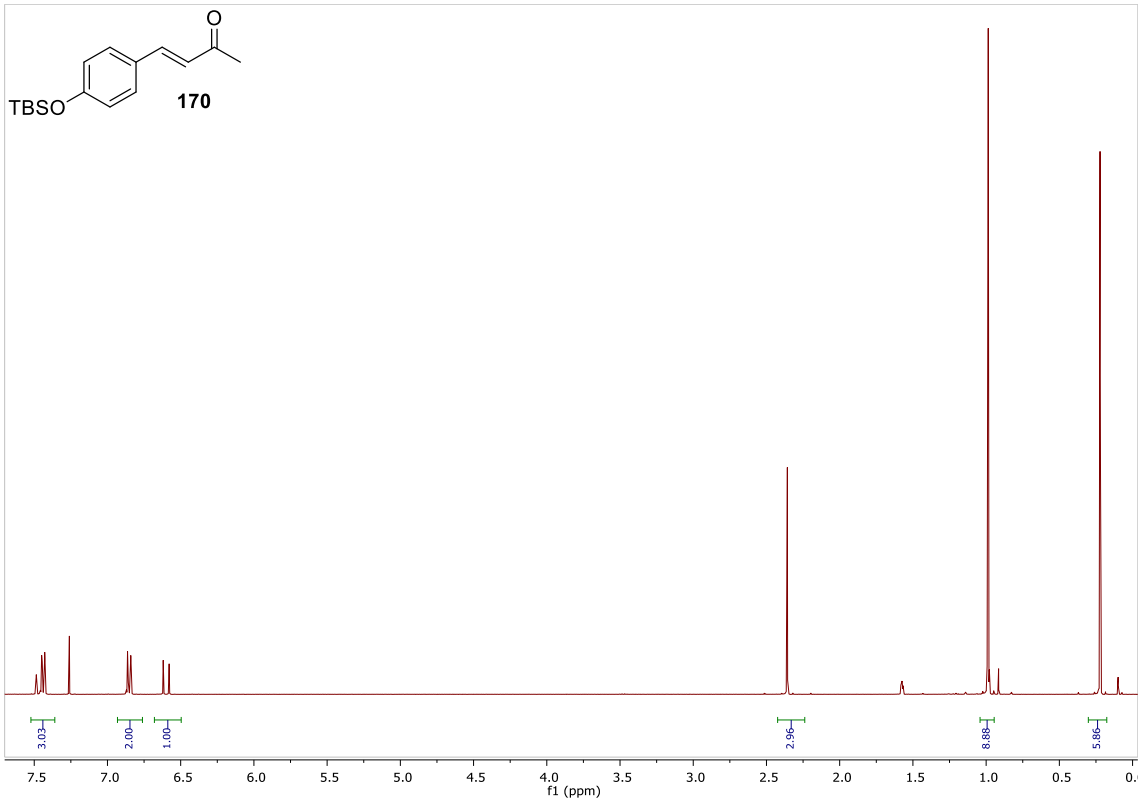

HO
OH
O
H
H
O
OH
OH
2.66
5.23
4.68
2.05
2.04
1.00
1.01
3.15
5.90
4.99
1.09
0.84
9.45
1.39
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

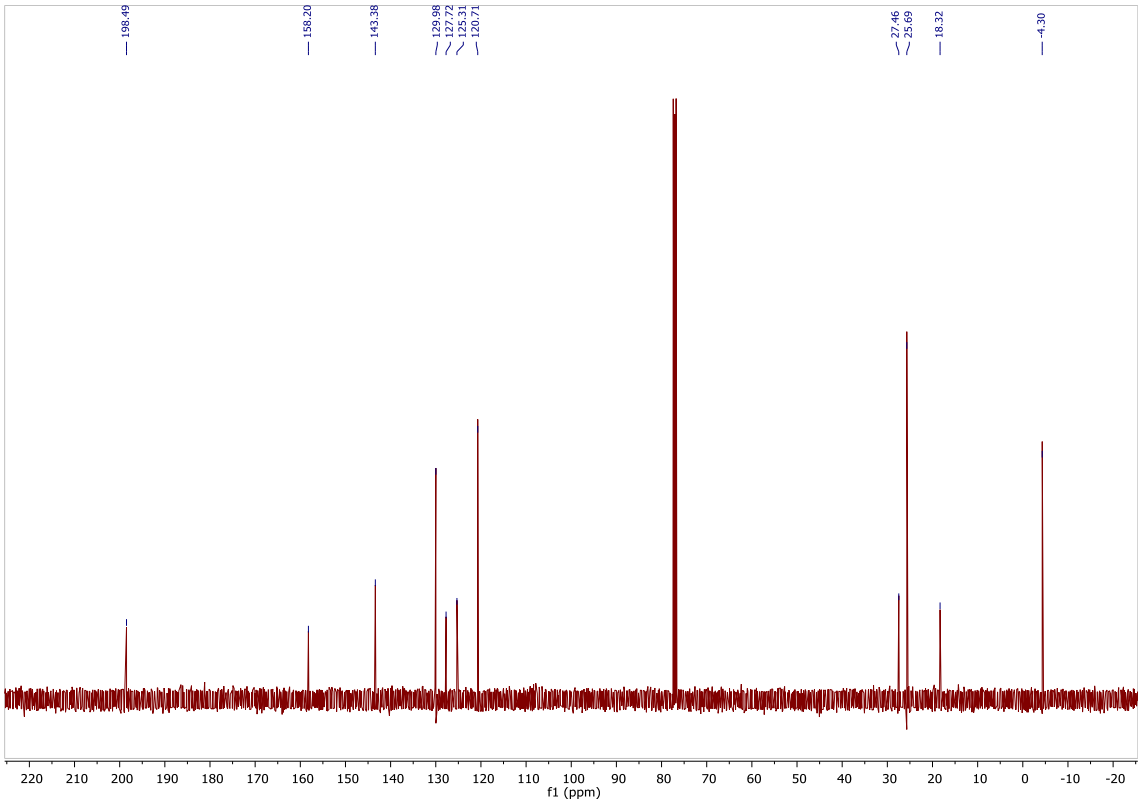
(+)-18

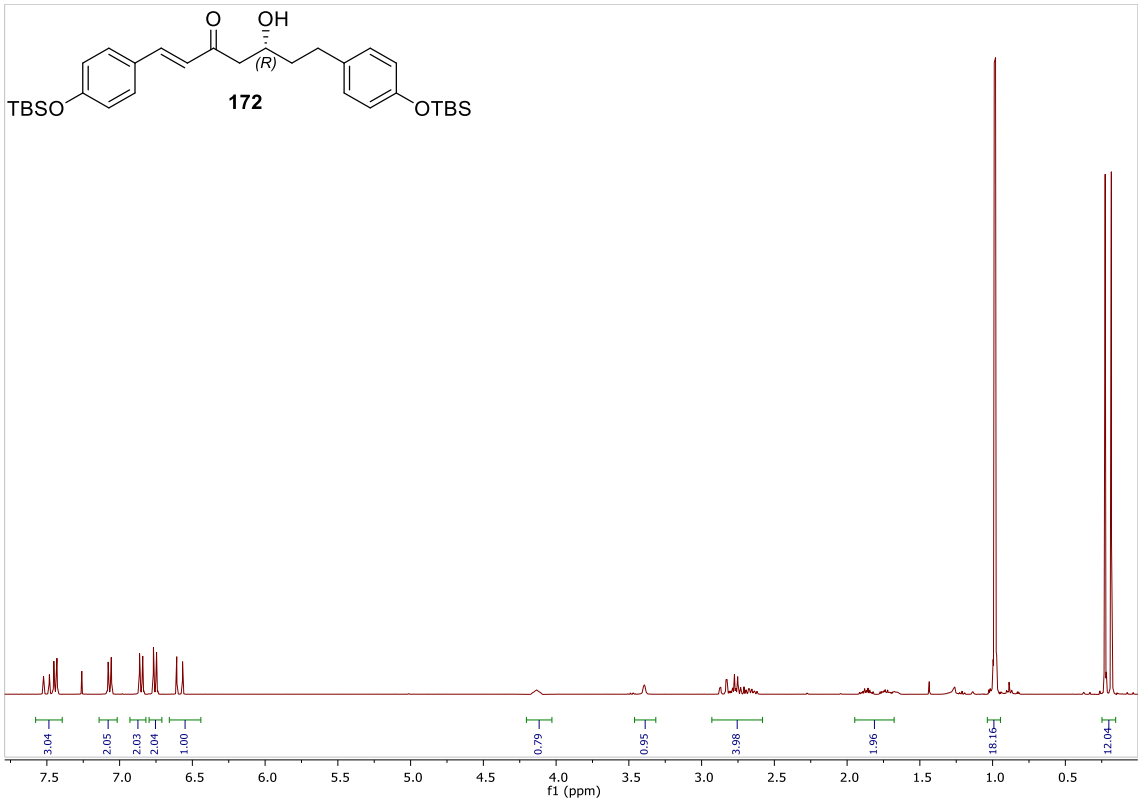

156.90
155.98
155.39
132.98
132.09
129.71
129.26
115.05
114.75
82.75
79.09
75.42
74.58
51.23
41.62
40.65
38.43
38.15
30.42
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
f1 (ppm)

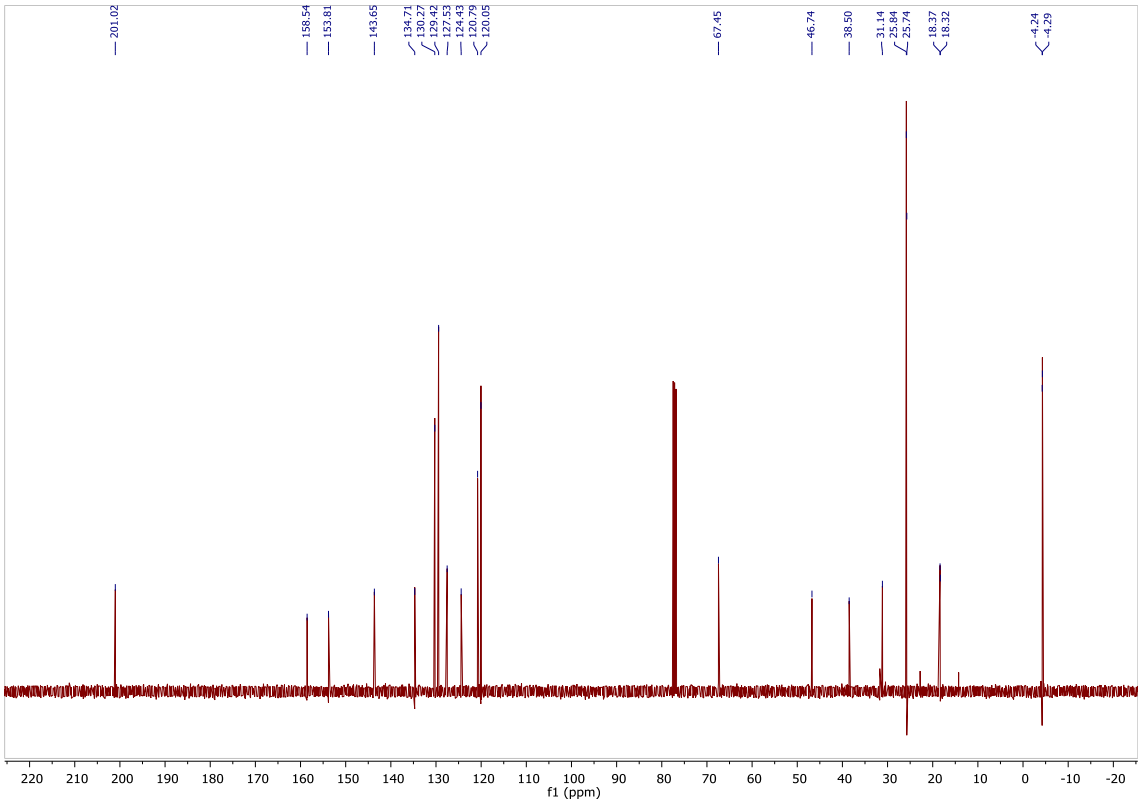

O
TBSO
171
1.00
2.09
2.09
2.09
2.08
9.32
6.18
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

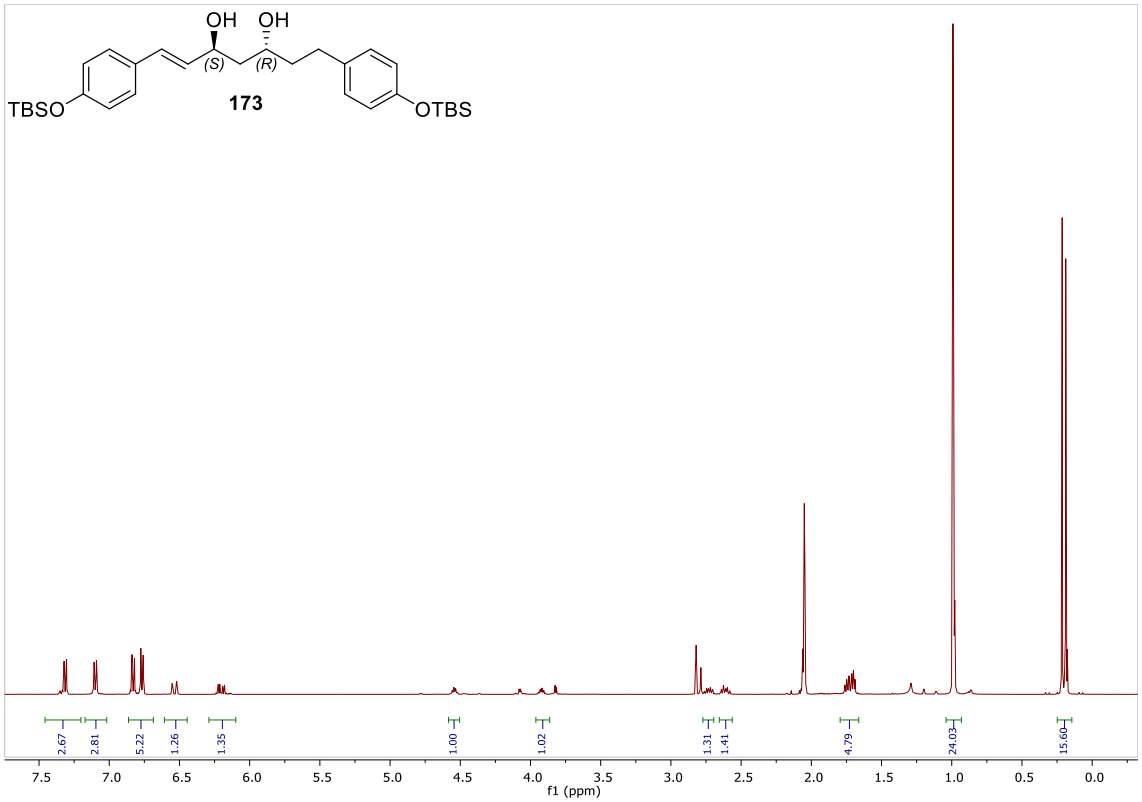

201.89
154.13
132.99
129.23
120.19
45.57
27.46
25.77
18.27
-4.35
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

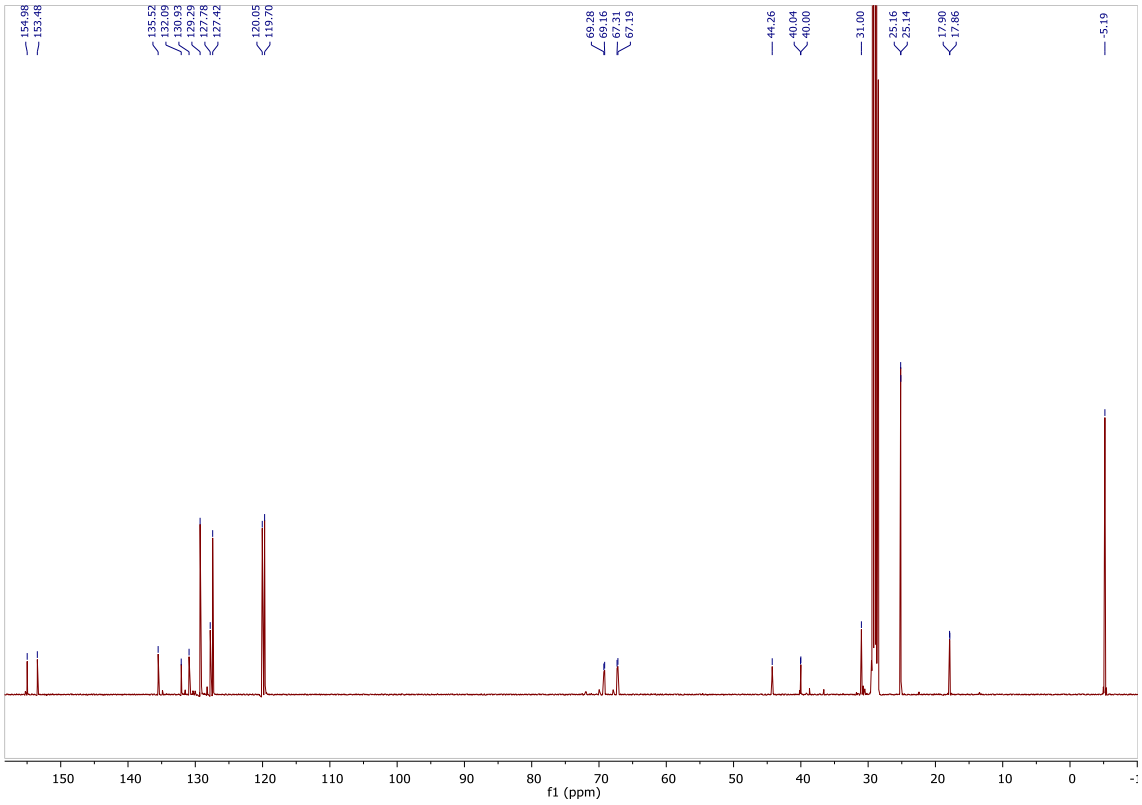

O
TBSO
170
3.03
2.00
1.00
2.96
8.88
5.86
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

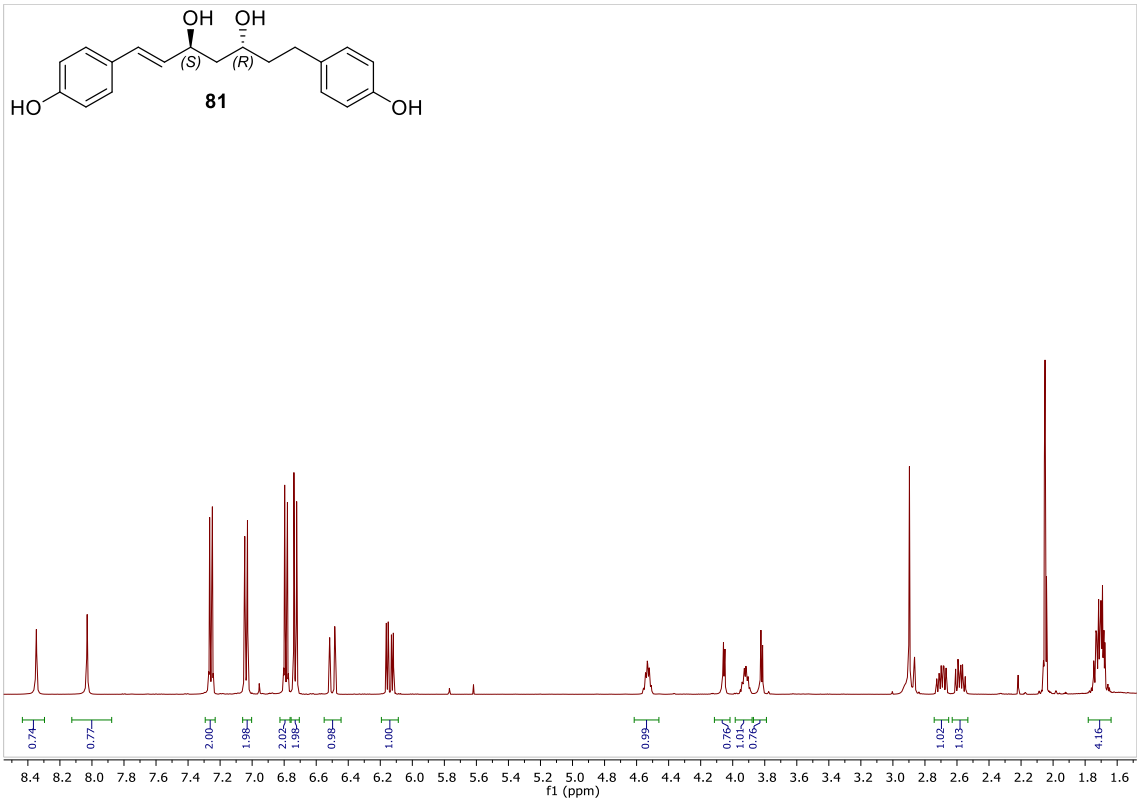

198.49
158.20
143.38
129.98
127.72
125.31
120.71
27.46
25.69
18.32
-4.30
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

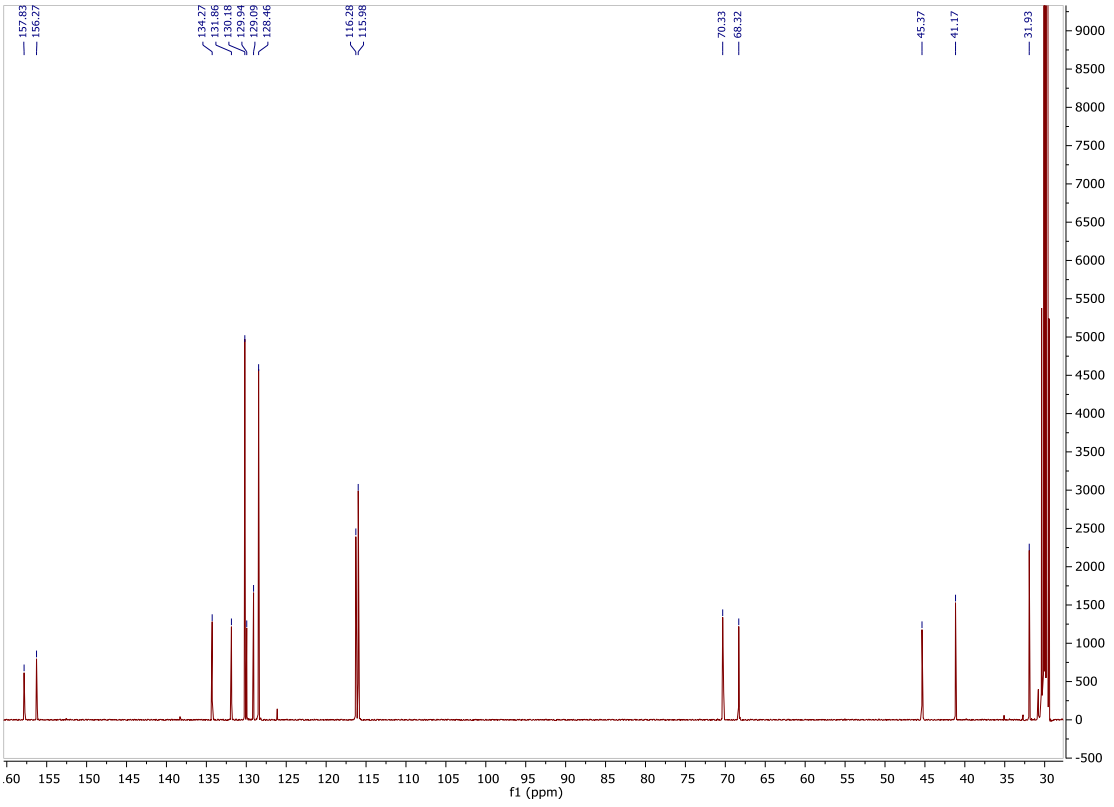

O
OH
(R)
TBSO
OTBS
172
3.04
2.05
2.03
2.04
1.00
0.79
0.95
3.98
1.96
18.16
12.04
f1 (ppm)

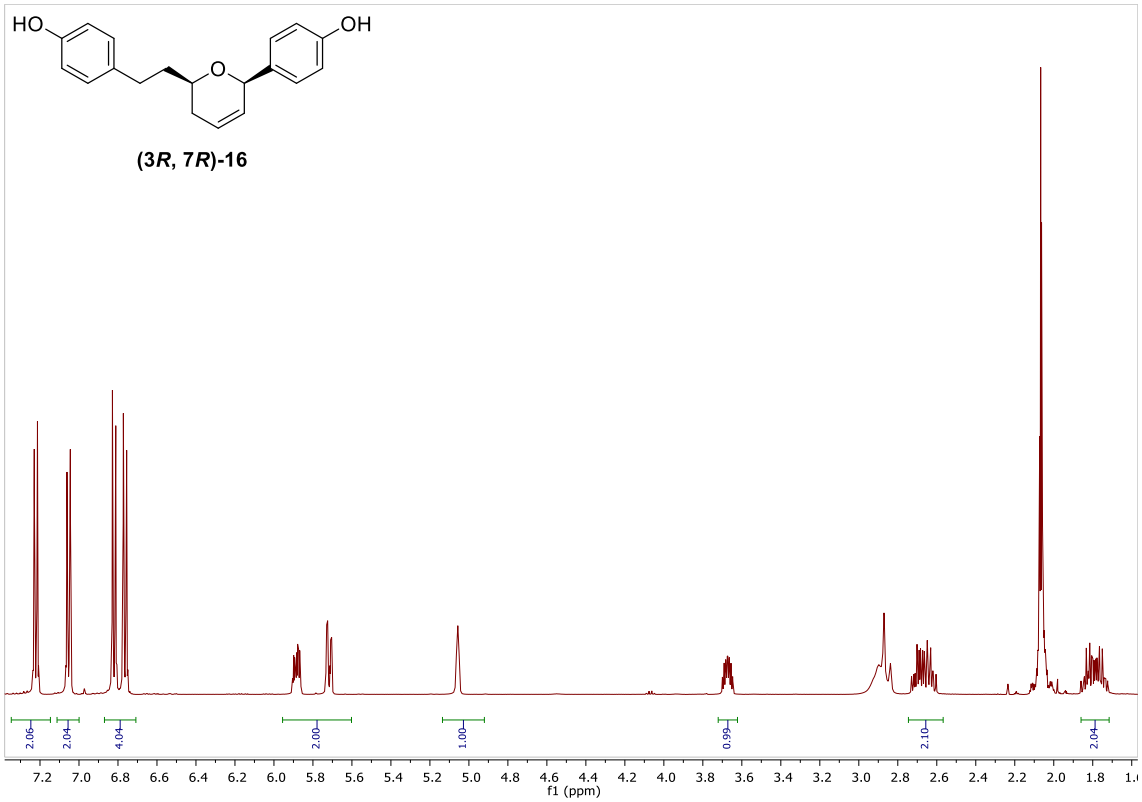

201.02
158.54
153.81
143.65
134.71
130.27
129.42
127.53
124.43
120.79
120.05
67.45
46.74
38.50
31.14
25.84
25.74
18.37
18.32
-4.24
-4.29
f1 (ppm)

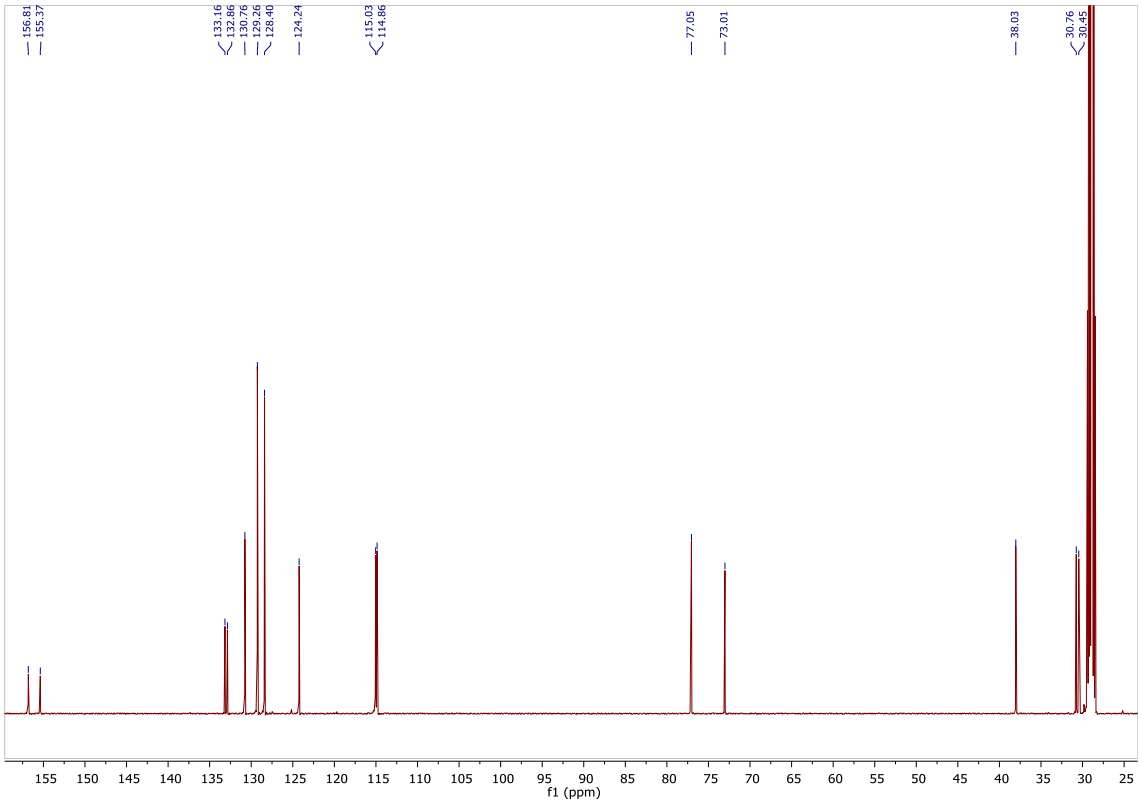

OH
OH
(S)
(R)
TBSO
OTBS
173
2.67
2.81
5.22
1.26
1.35
1.00
1.02
1.31
1.41
4.79
24.03
15.60
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

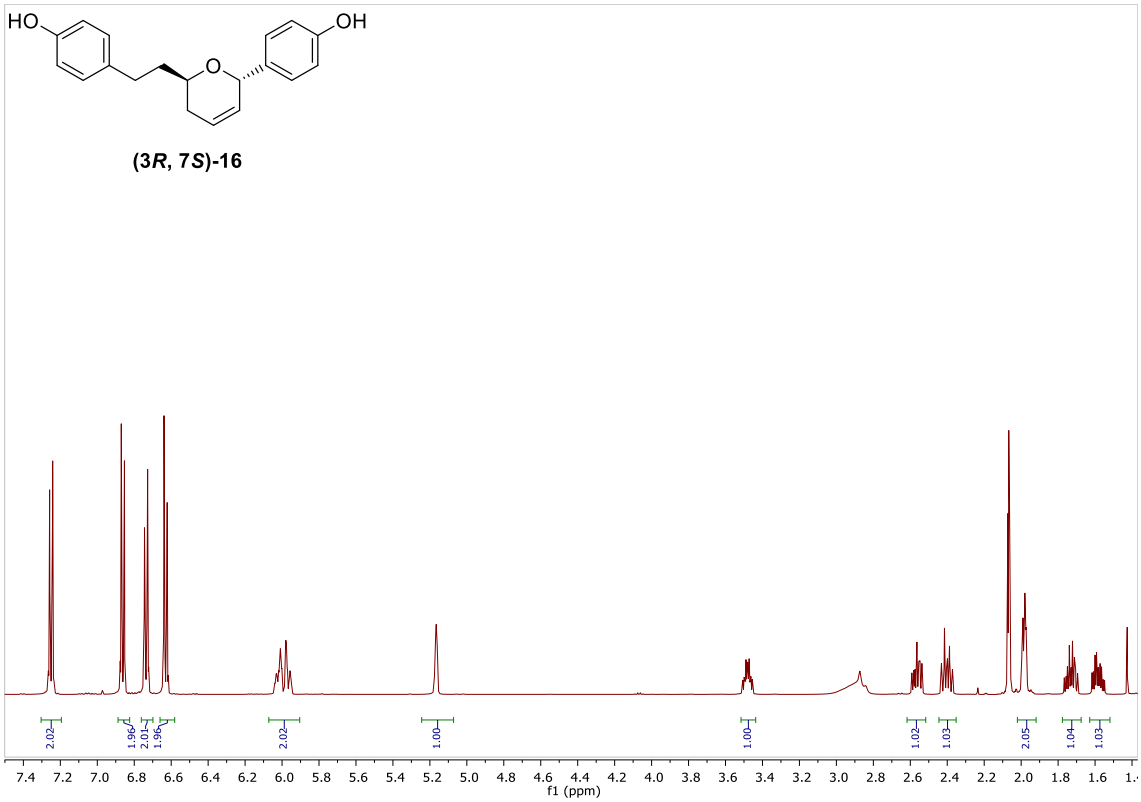

154.98
153.48
135.52
132.09
130.93
129.29
127.78
127.42
120.05
119.70
69.28
69.16
67.31
67.19
44.26
40.04
40.00
31.00
25.16
25.14
17.90
17.86
-5.19
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OH
OH
(S)
(R)
HO
OH
81
f1 (ppm)

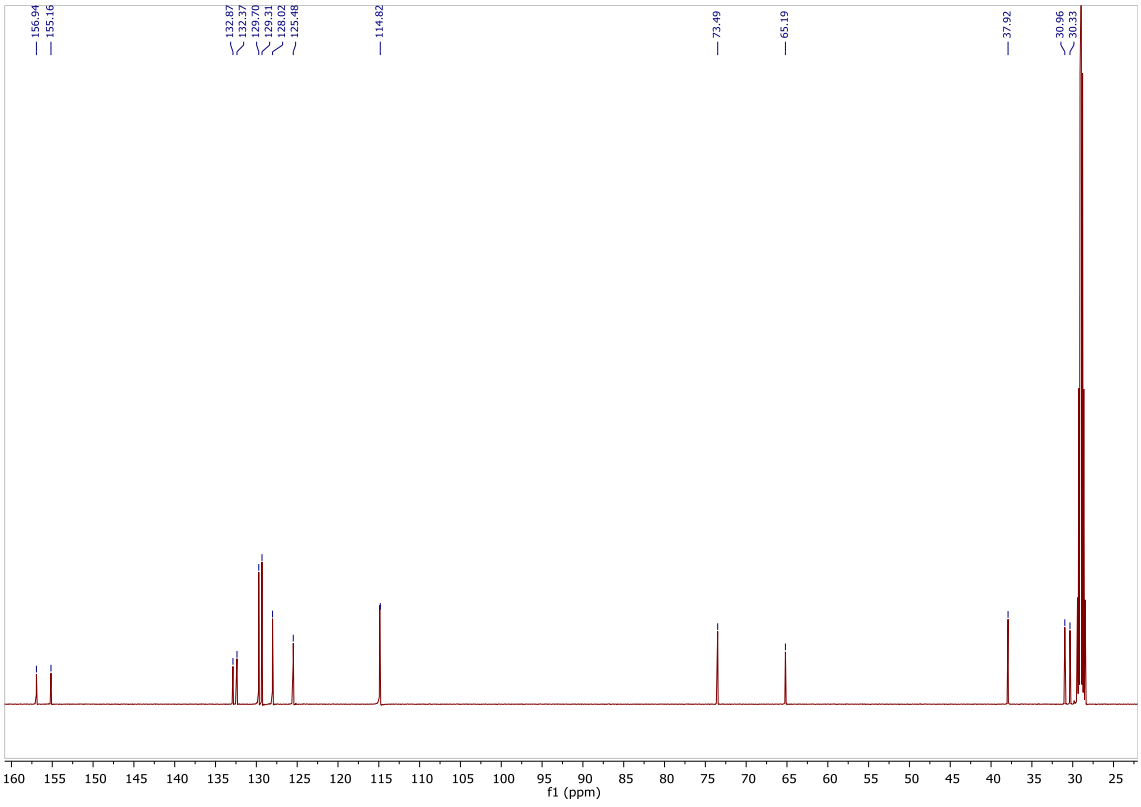

157.83
156.27
134.27
131.86
130.18
129.94
129.09
128.46
116.28
115.98
70.33
68.32
45.37
41.17
31.93
f1 (ppm)


HO
OH
O
(3R, 7R)-16
2.06
2.04
4.04
2.00
1.00
0.99
2.10
2.04
f1 (ppm)

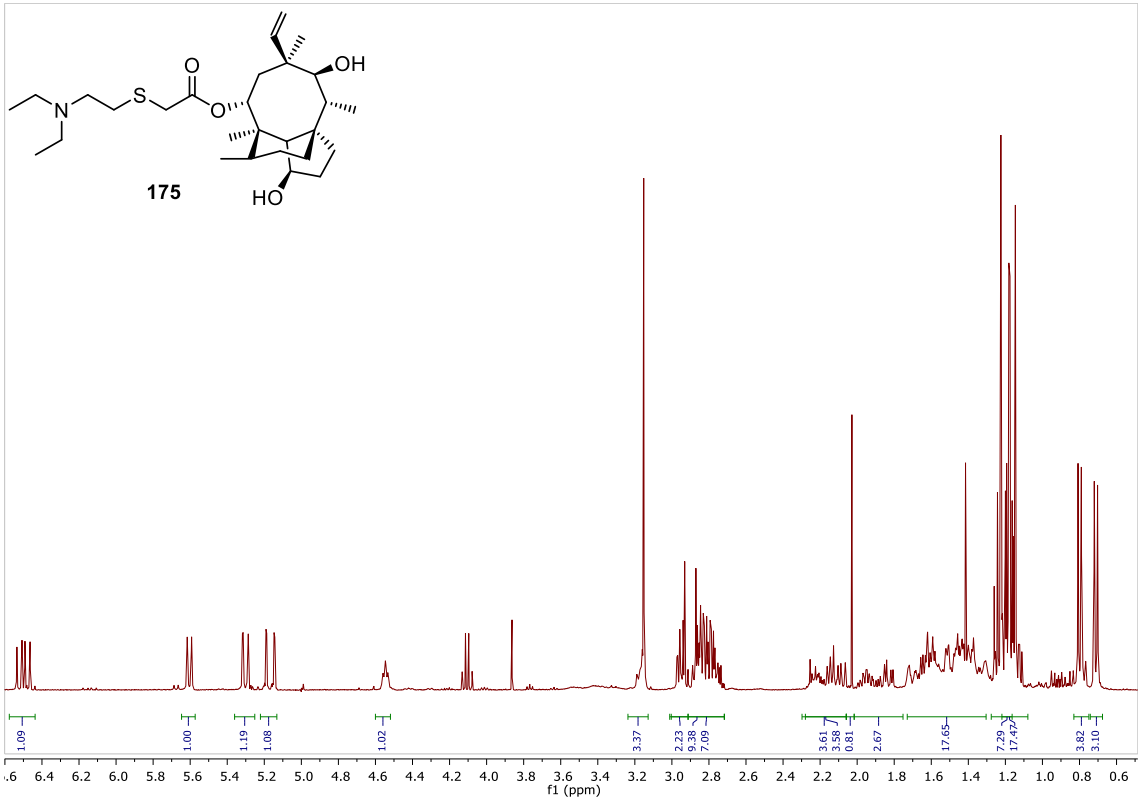

156.81
155.37
133.16
132.86
130.76
129.26
128.40
124.24
115.03
114.86
77.05
73.01
38.03
30.76
30.45
f1 (ppm)

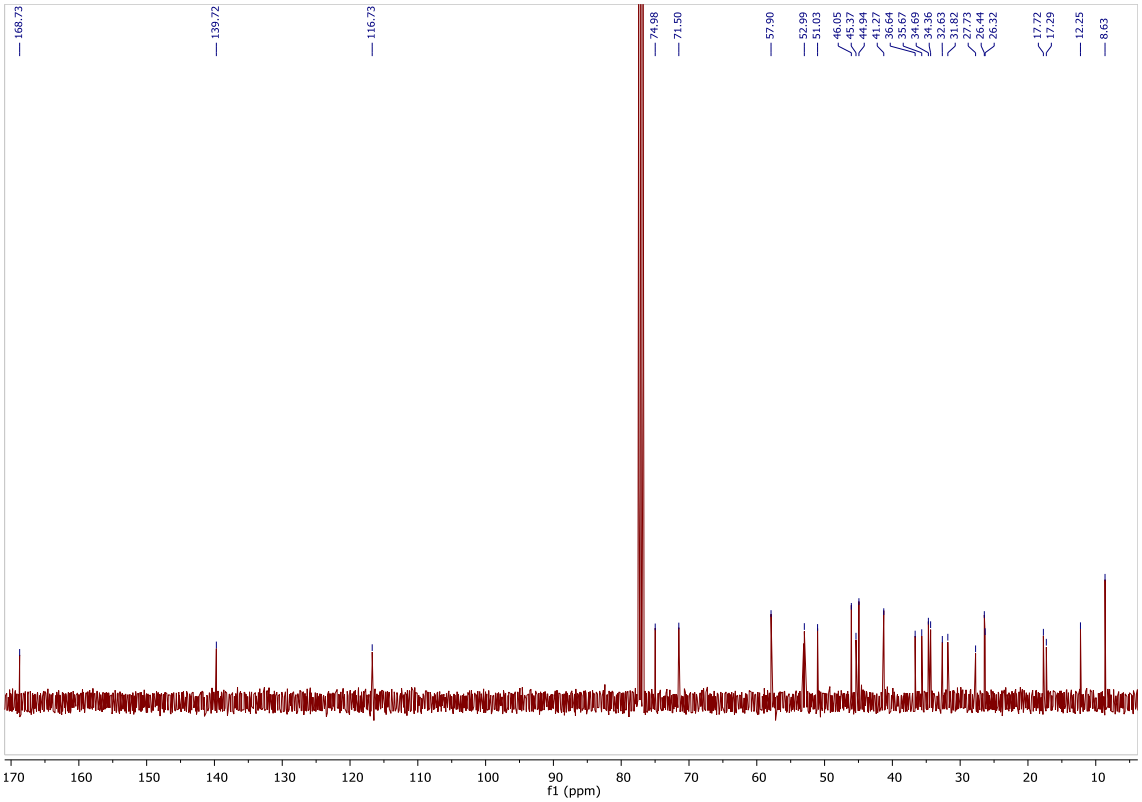

HO
OH
O
2.02
1.96
2.01
1.96
2.02
1.00
1.00
1.02
1.03
2.05
1.04
1.03
f1 (ppm)

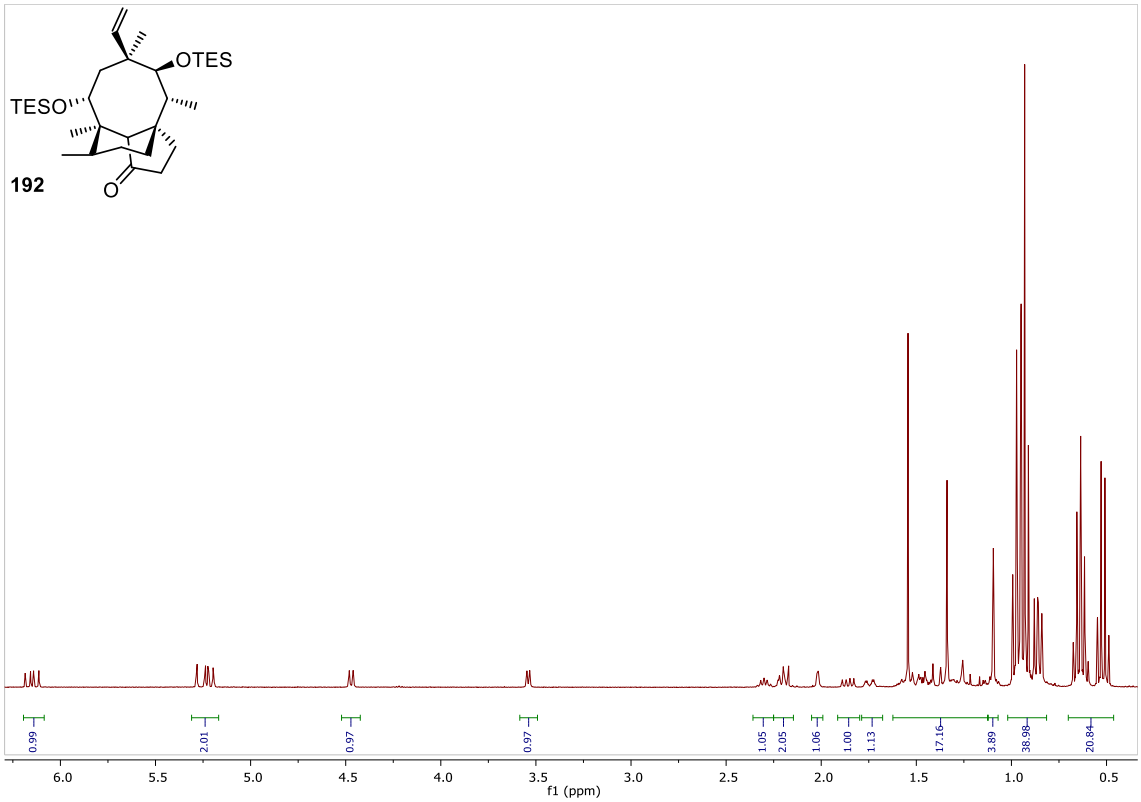
(3*R*, 7*S*)-16

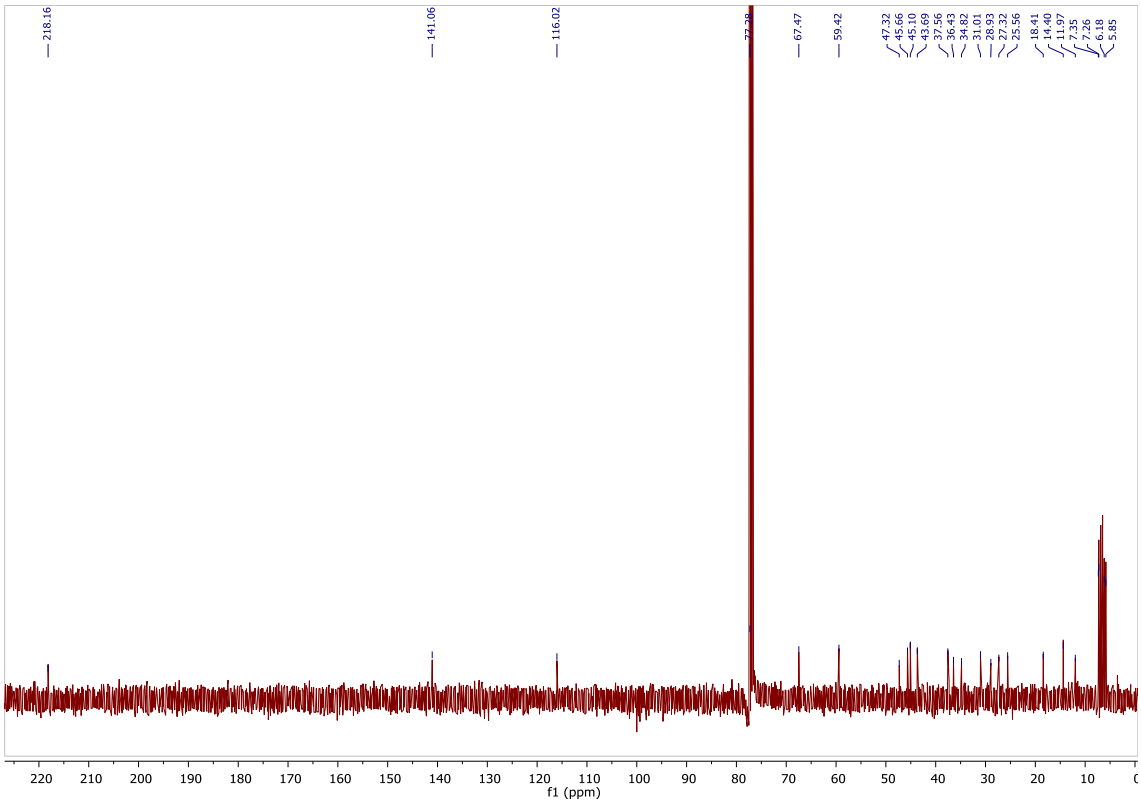

156.94
155.16
132.87
132.37
129.70
129.31
128.02
125.48
114.82
73.49
65.19
37.92
30.96
30.33
f1 (ppm)

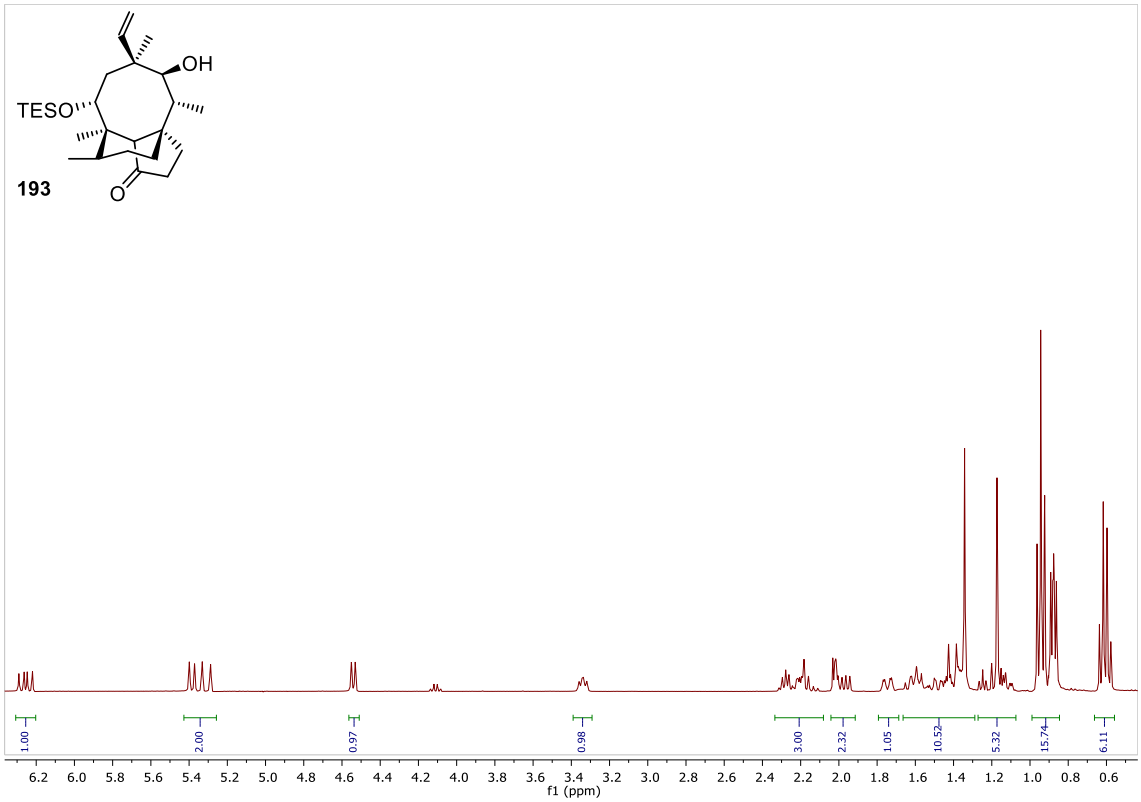
5.2 NMR Spectra pertaining to chapter 2

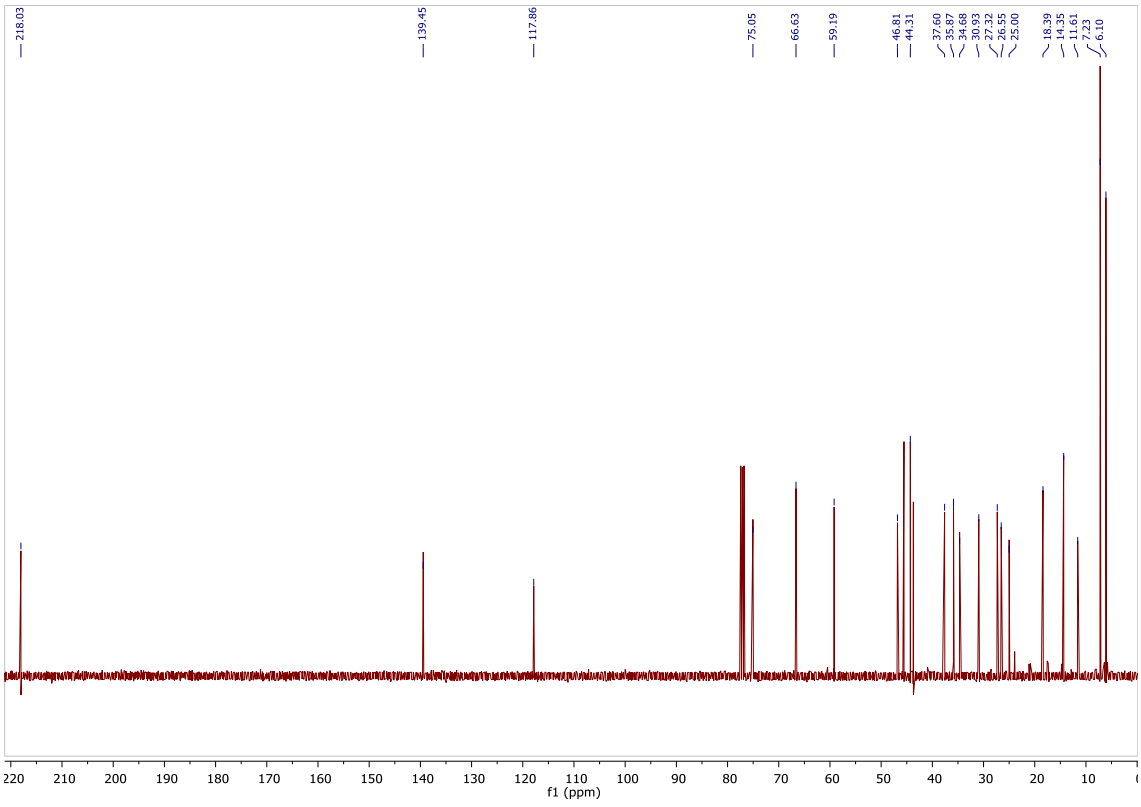


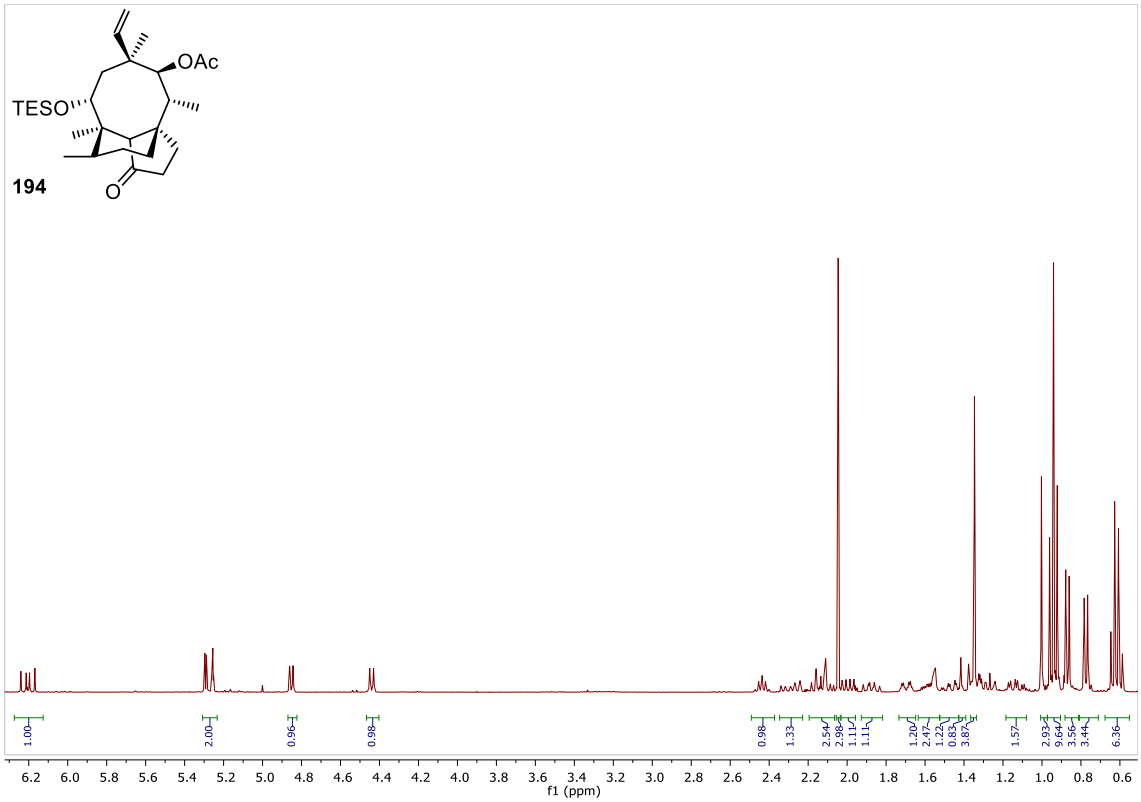


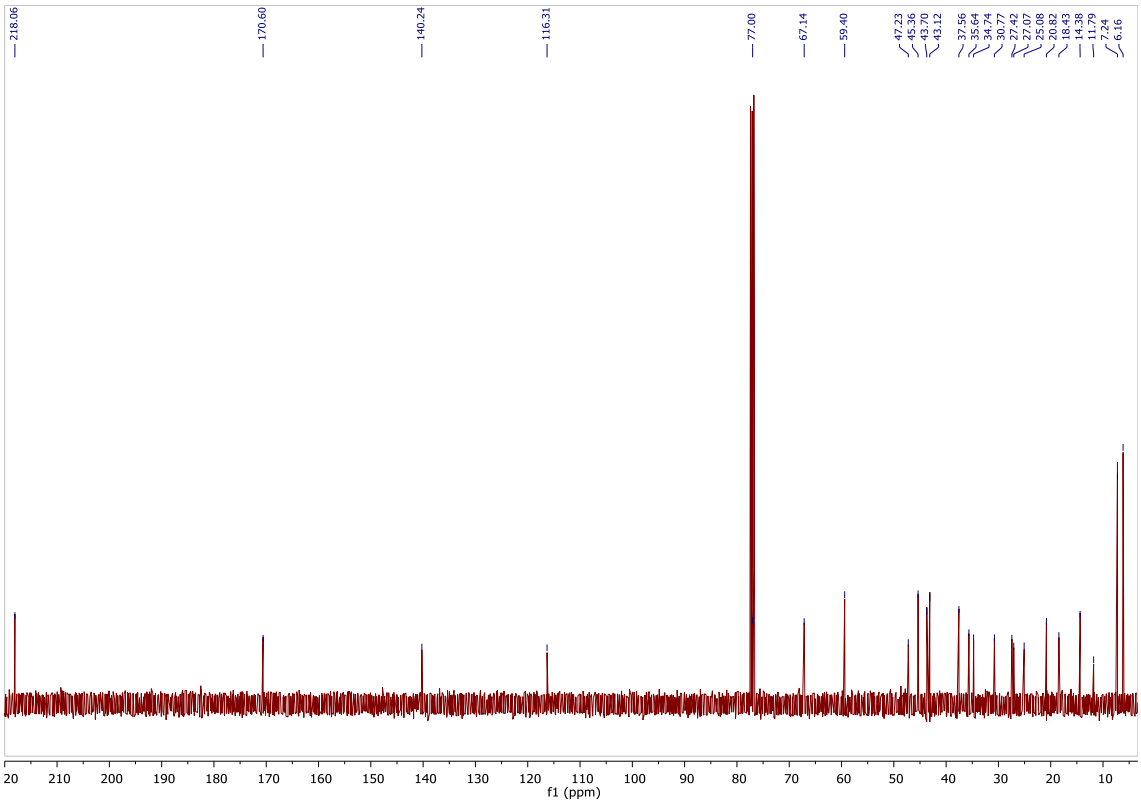

OTES
TESO
O
192
0.99
2.01
0.97
0.97
1.05
2.05
1.06
1.00
1.13
17.16
3.89
38.98
20.84
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

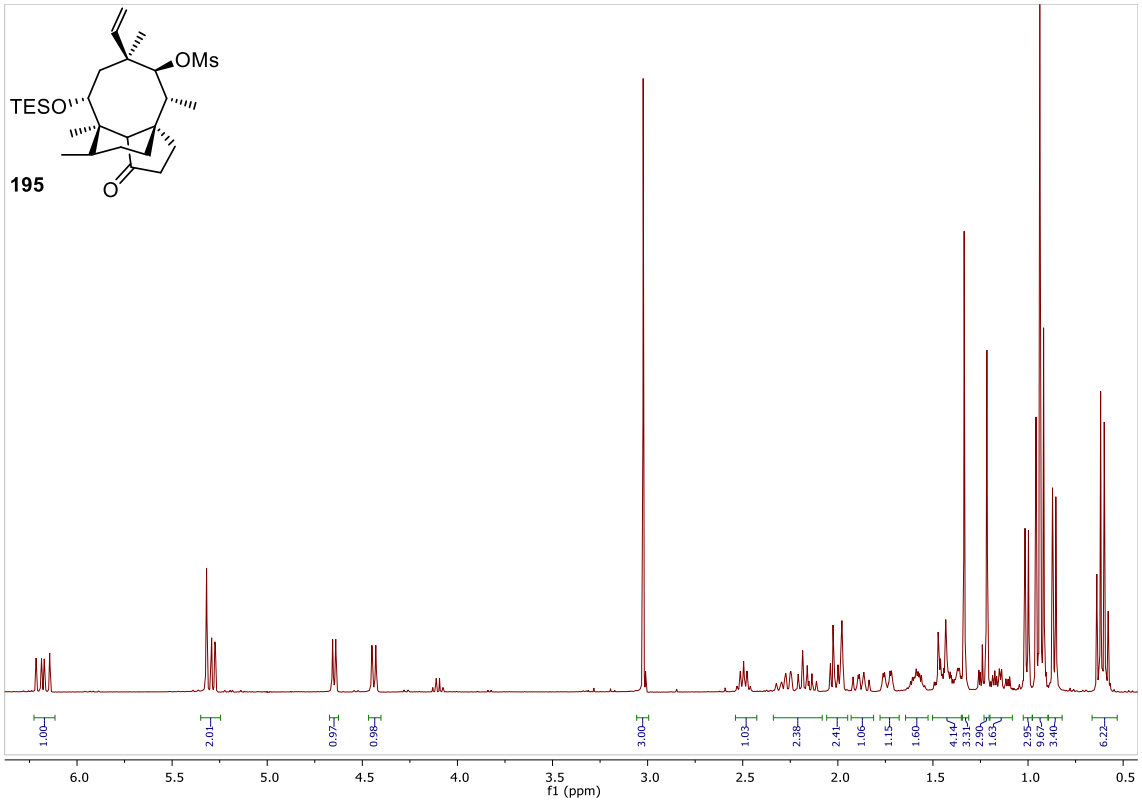

218.16
141.06
116.02
77.38
67.47
59.42
47.32
45.66
45.10
43.69
37.56
36.43
34.82
31.01
28.93
27.32
25.56
18.41
14.40
11.97
7.35
7.26
6.18
5.85
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

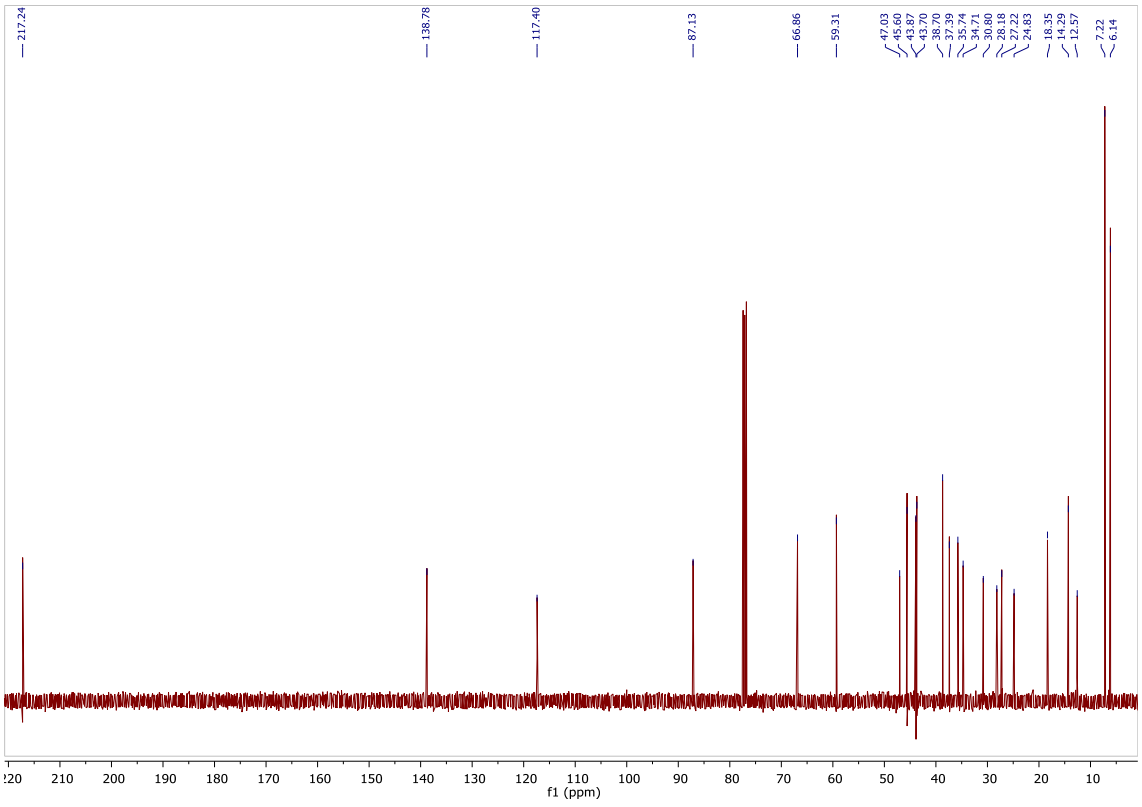

OH
TESO
O
193
1.00
2.00
0.97
0.98
3.00
2.32
1.05
10.52
5.32
15.74
6.11
f1 (ppm)

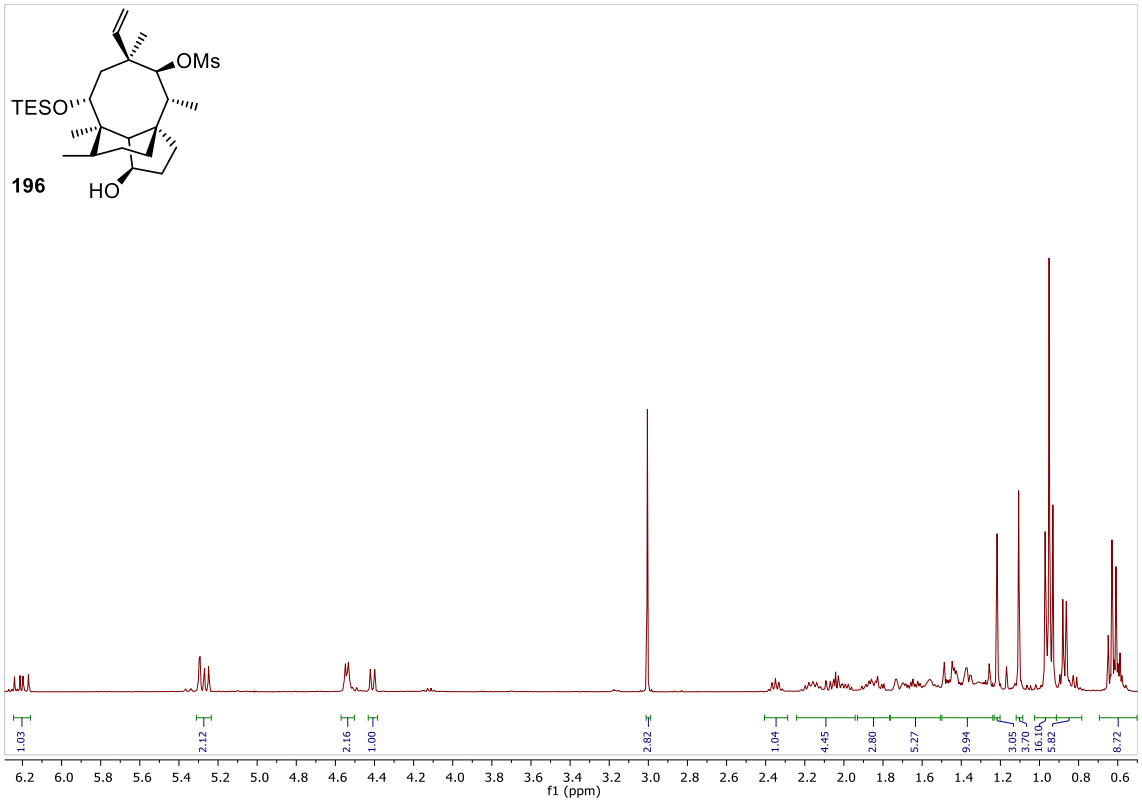

218.03
139.45
117.86
75.05
66.63
59.19
46.81
44.31
37.60
35.87
34.68
30.93
27.32
26.55
25.00
18.39
14.35
11.61
7.23
6.10
f1 (ppm)

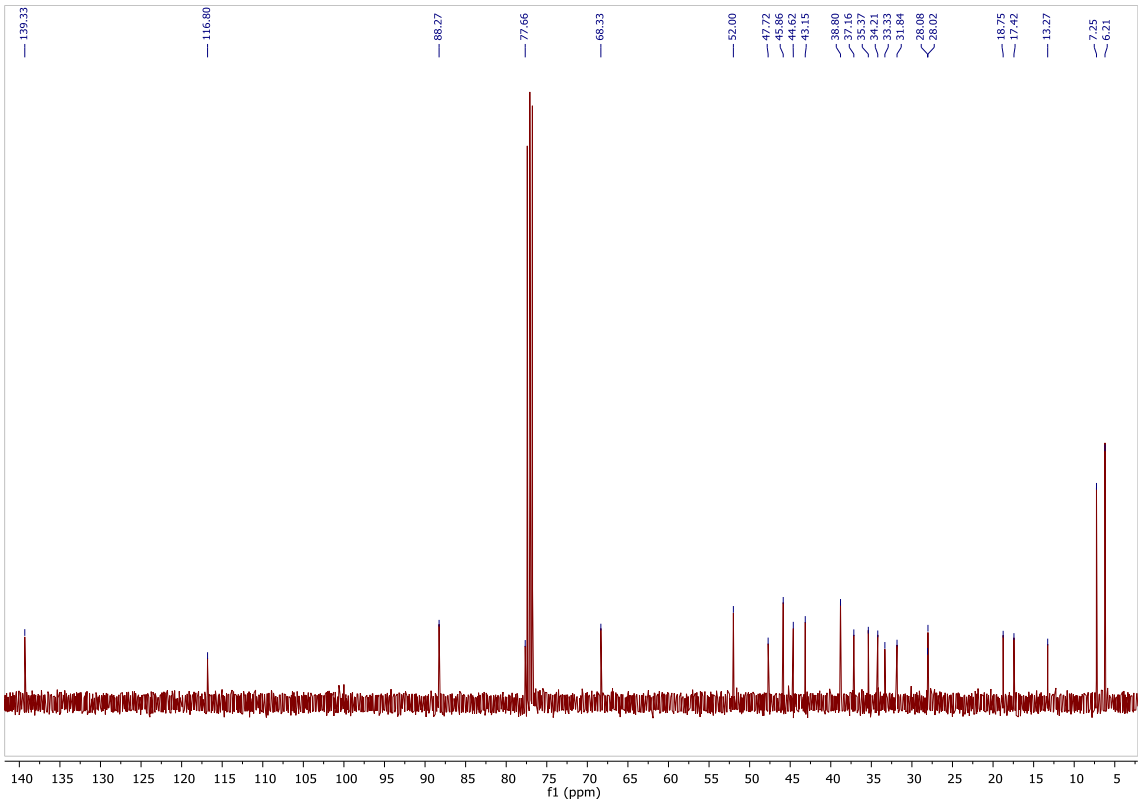

OAc
TESO
O
194
1.00
2.00
0.96
0.98
0.98
1.33
2.54
2.98
1.11
1.11
1.20
2.47
1.22
0.83
3.87
1.57
2.93
9.64
3.56
3.44
6.36
6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f1 (ppm)

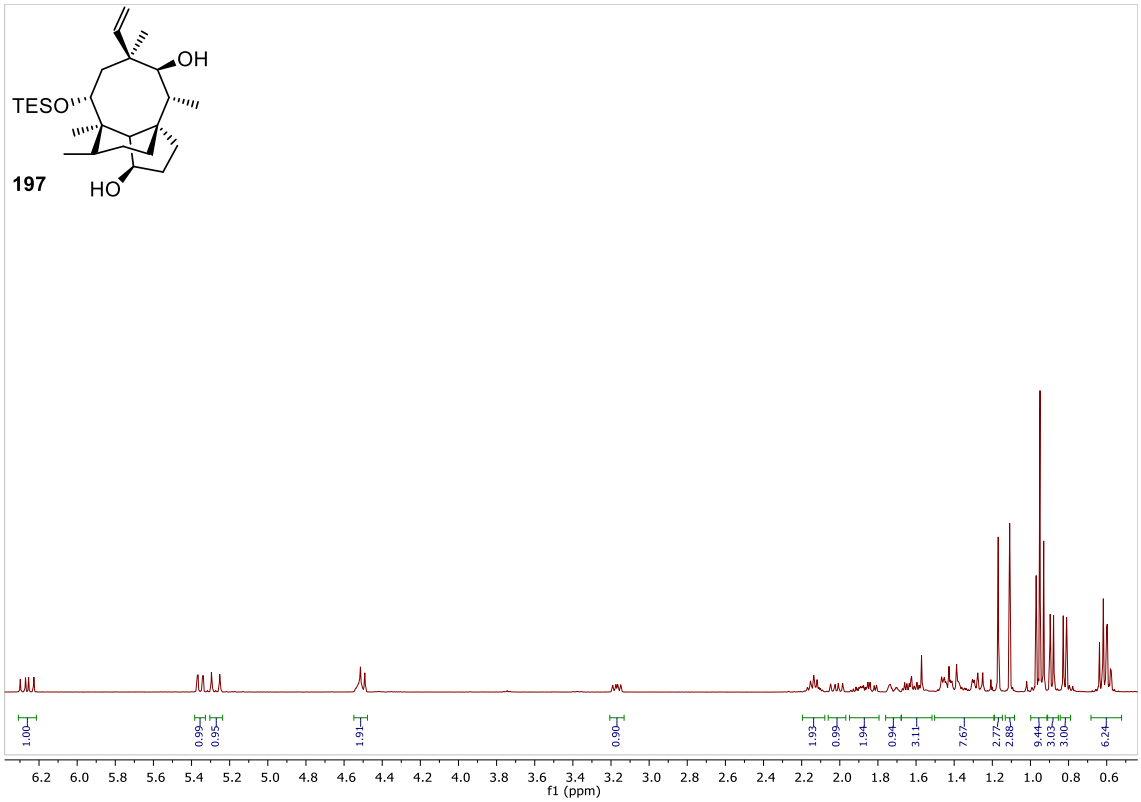

218.06
170.60
140.24
116.31
77.00
67.14
59.40
47.23
45.36
43.70
43.12
37.56
35.64
34.74
30.77
27.42
27.07
25.08
20.82
18.43
14.38
11.79
7.24
6.16
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

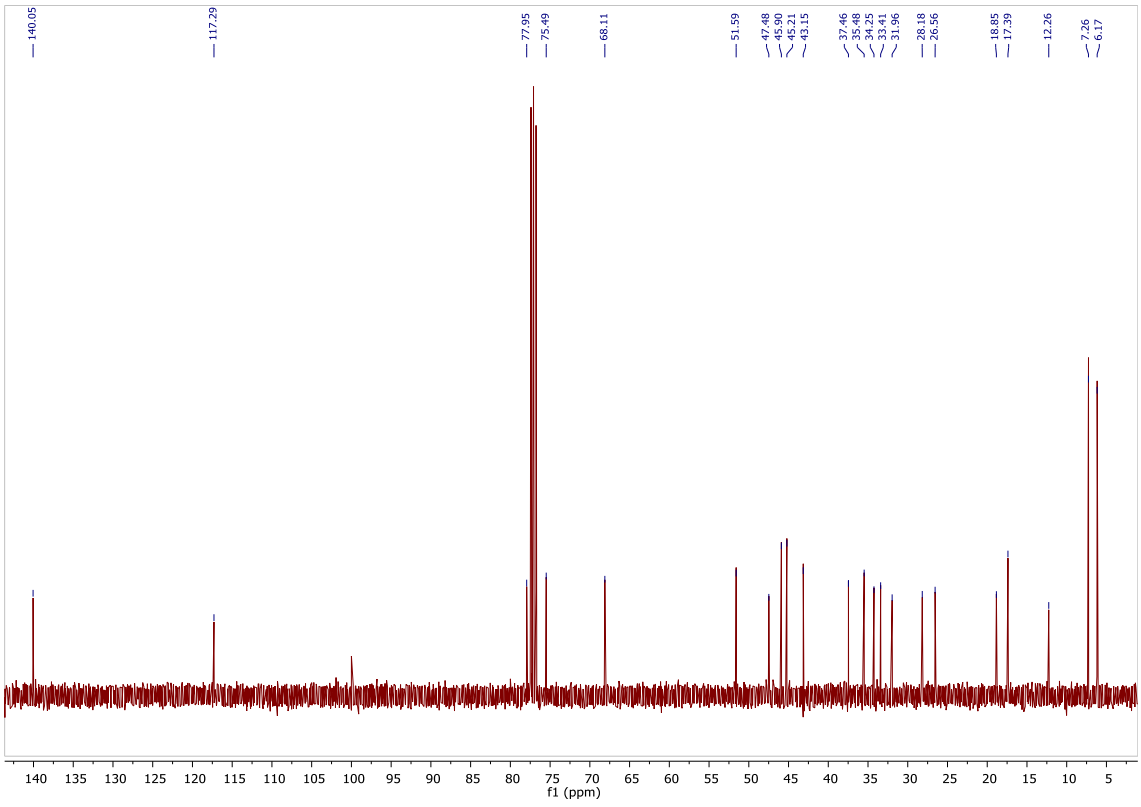

OMs
TESO
O
195
1.00
2.01
0.97
0.98
3.00
1.03
2.38
2.41
1.06
1.15
1.60
4.14
3.31
2.90
1.63
2.95
9.67
3.40
6.22
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

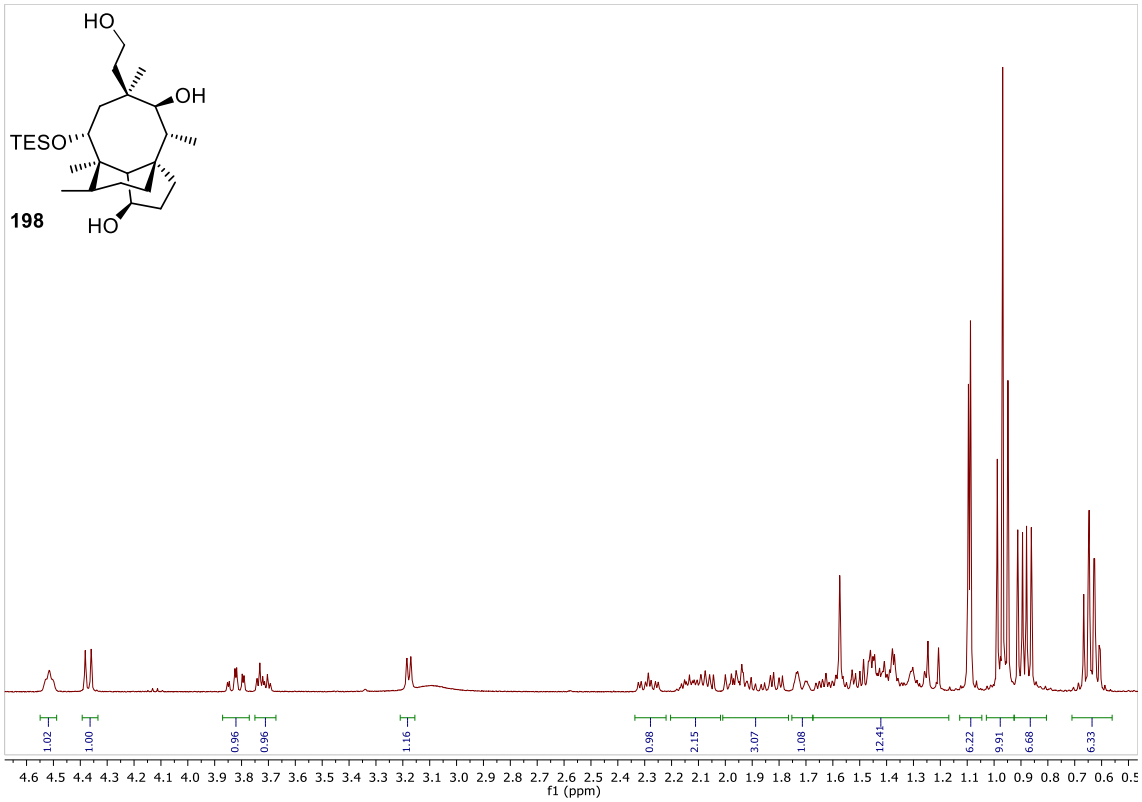

217.24
138.78
117.40
87.13
66.86
59.31
47.03
45.60
43.87
43.70
38.70
37.39
35.74
34.71
30.80
28.18
27.22
24.83
18.35
14.29
12.57
7.22
6.14
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

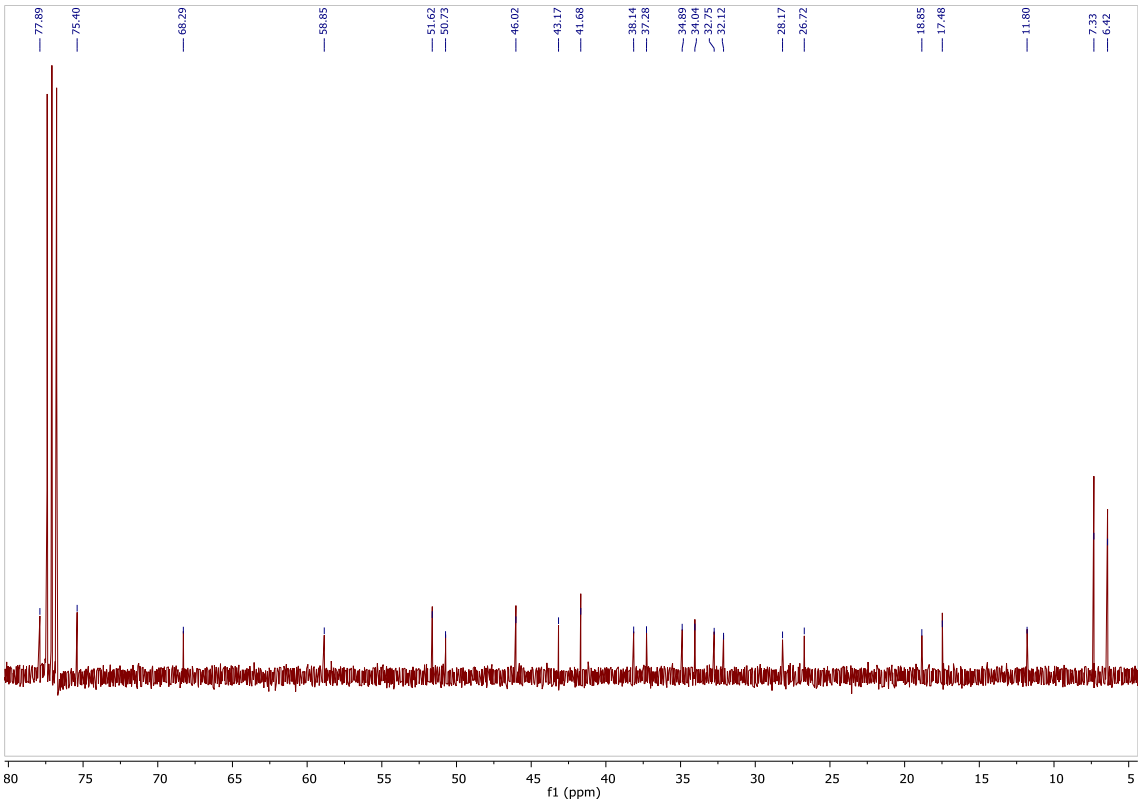

OMs
TESO
196
HO
1.03
2.12
2.16
1.00
2.82
1.04
4.45
2.80
5.27
9.94
3.05
3.70
16.10
5.82
8.72
f1 (ppm)

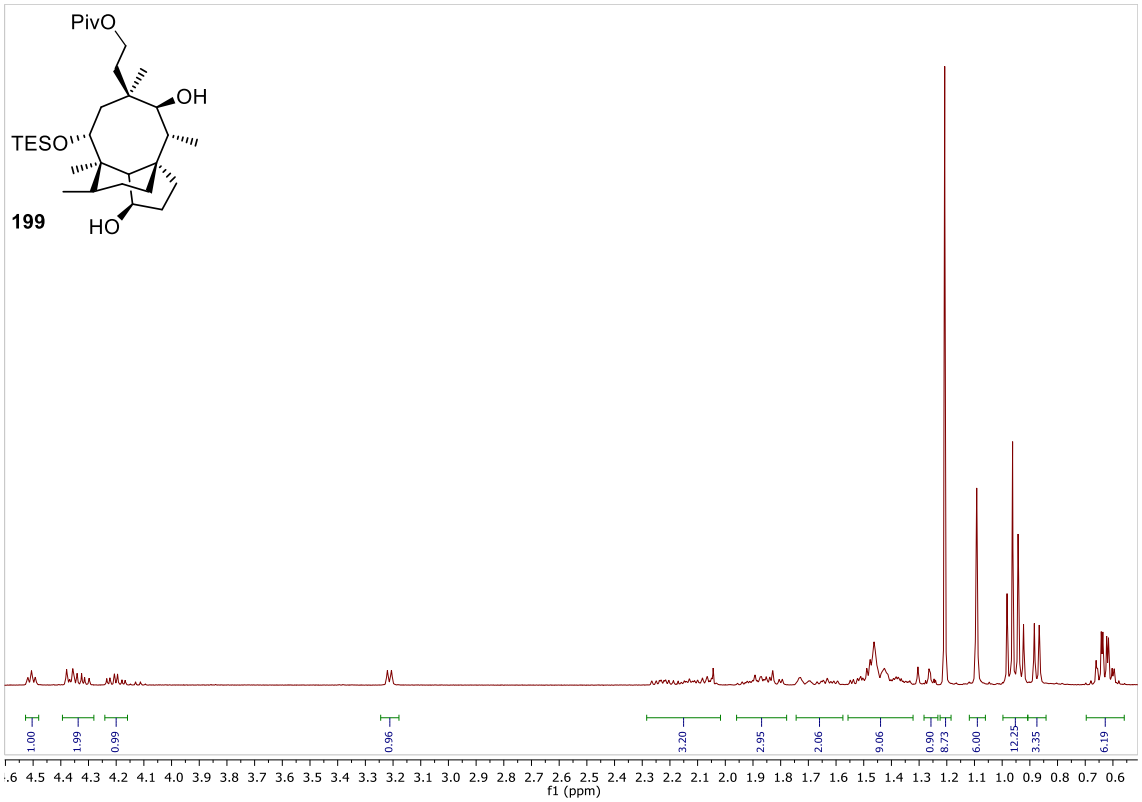

139.33
116.80
88.27
77.66
68.33
52.00
47.72
45.86
44.62
43.15
38.80
37.16
35.37
34.21
33.33
31.84
28.08
28.02
18.75
17.42
13.27
7.25
6.21
f1 (ppm)

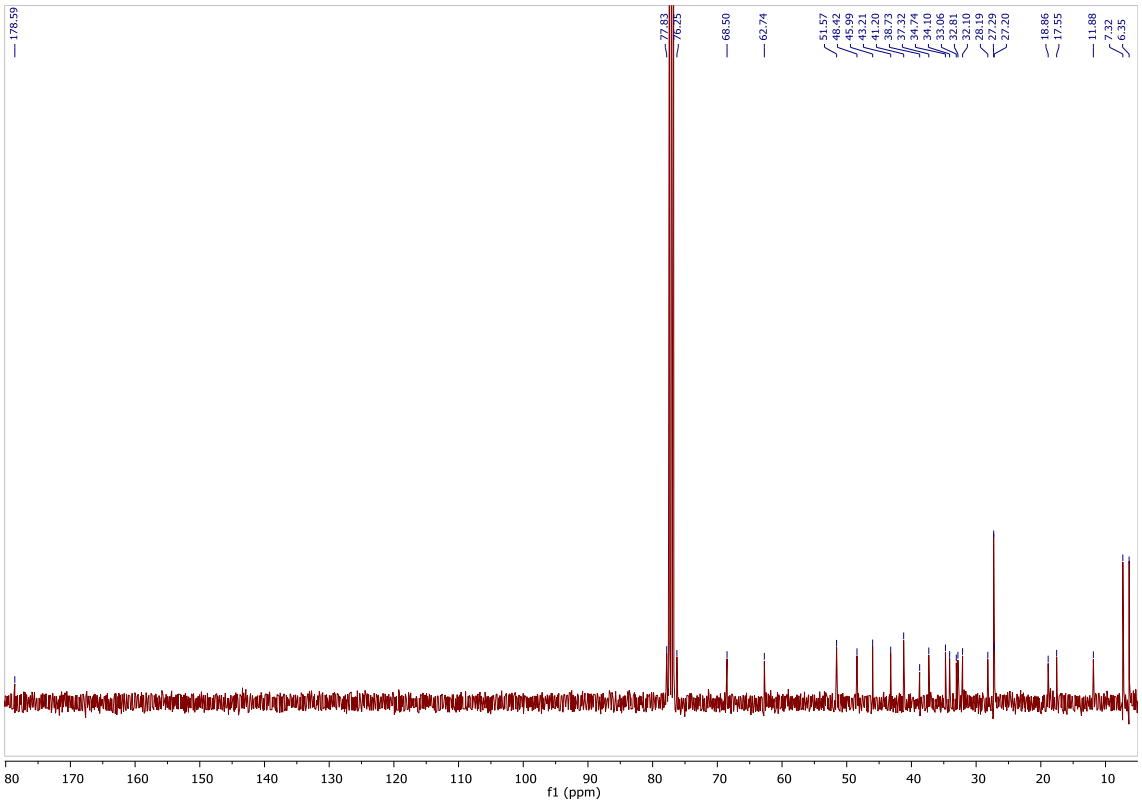

OH
TESO
HO
197
1.00
0.99
0.95
1.91
0.90
1.93
0.99
1.94
0.94
3.11
7.67
2.77
2.88
9.44
3.03
3.00
6.24
f1 (ppm)

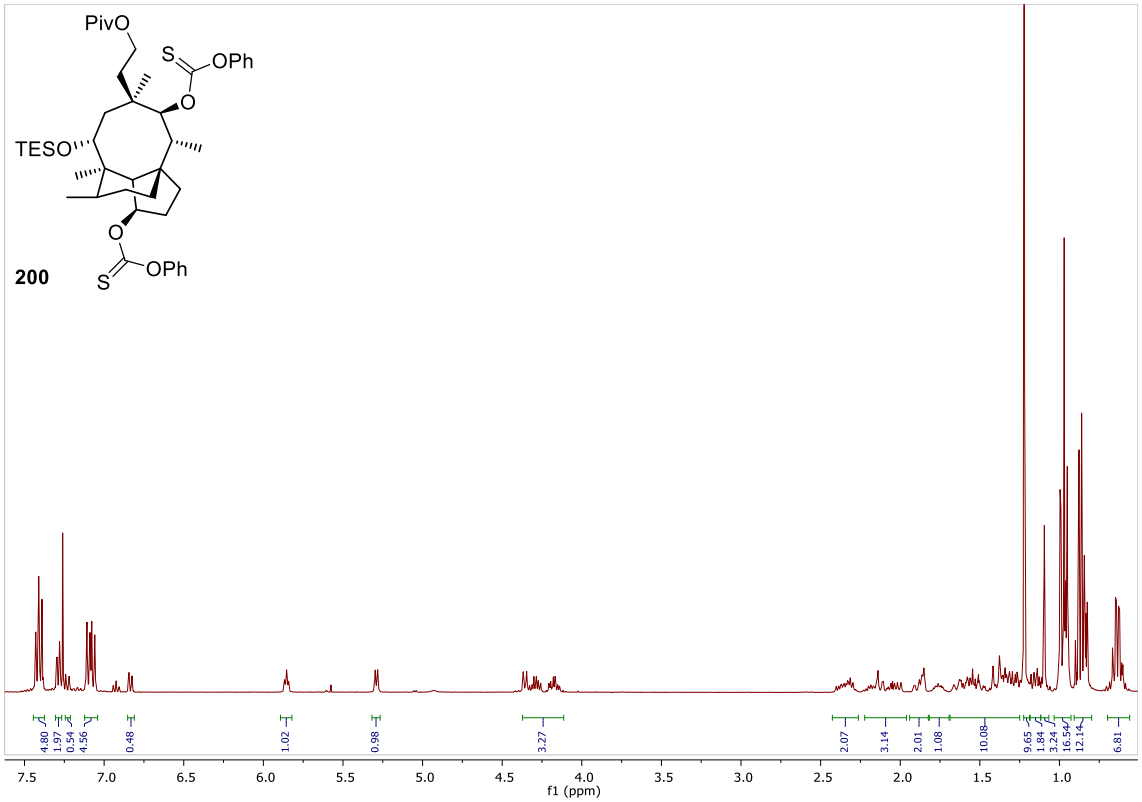

140.05
117.29
77.95
75.49
68.11
51.59
47.48
45.90
45.21
43.15
37.46
35.48
34.25
33.41
31.96
28.18
26.56
18.85
17.39
12.26
7.26
6.17
f1 (ppm)

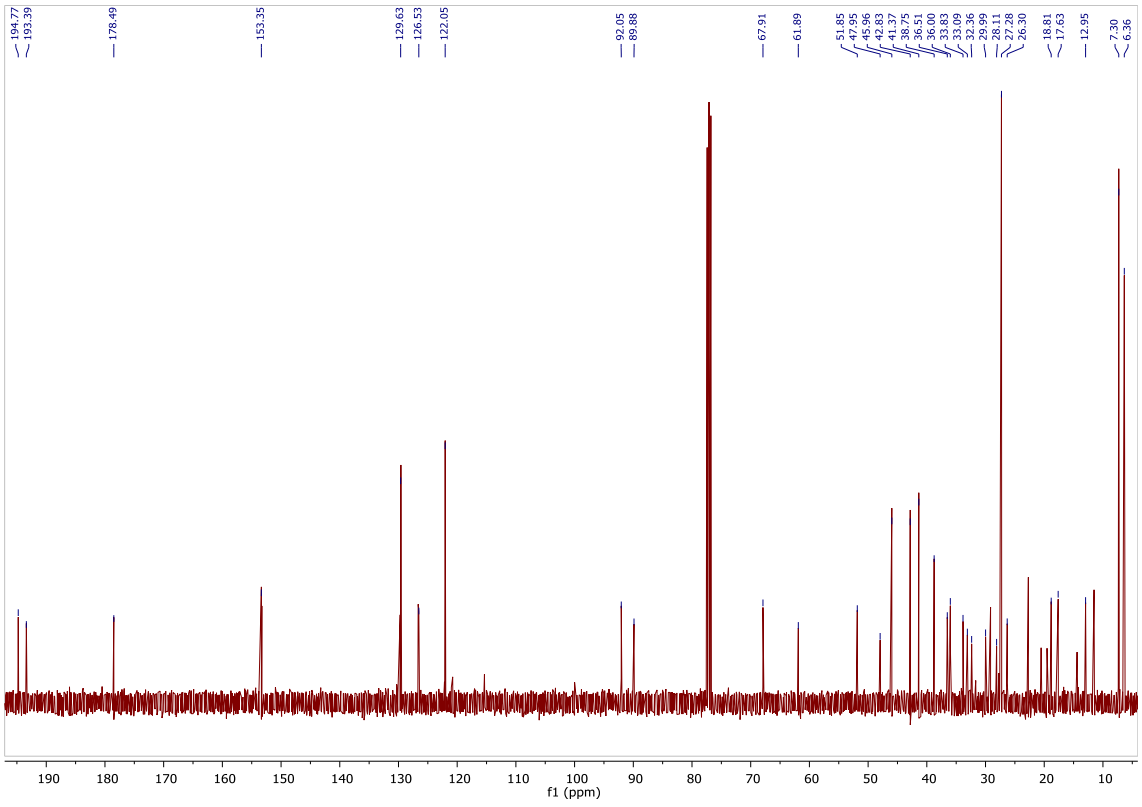

HO
OH
TESO
198
HO
1.02
1.00
0.96
0.96
1.16
0.98
2.15
3.07
1.08
12.41
6.22
9.91
6.68
6.33
f1 (ppm)

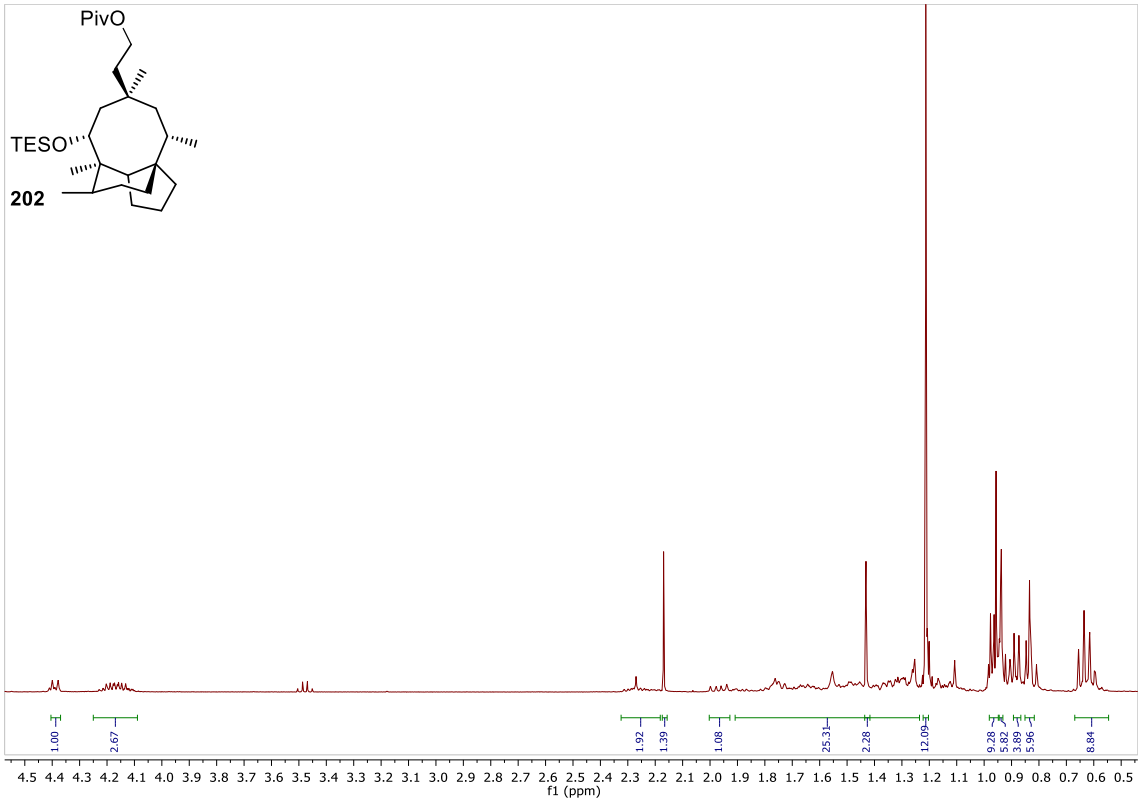

77.89
75.40
68.29
58.85
51.62
50.73
46.02
43.17
41.68
38.14
37.28
34.89
34.04
32.75
32.12
28.17
26.72
18.85
17.48
11.80
7.33
6.42
f1 (ppm)

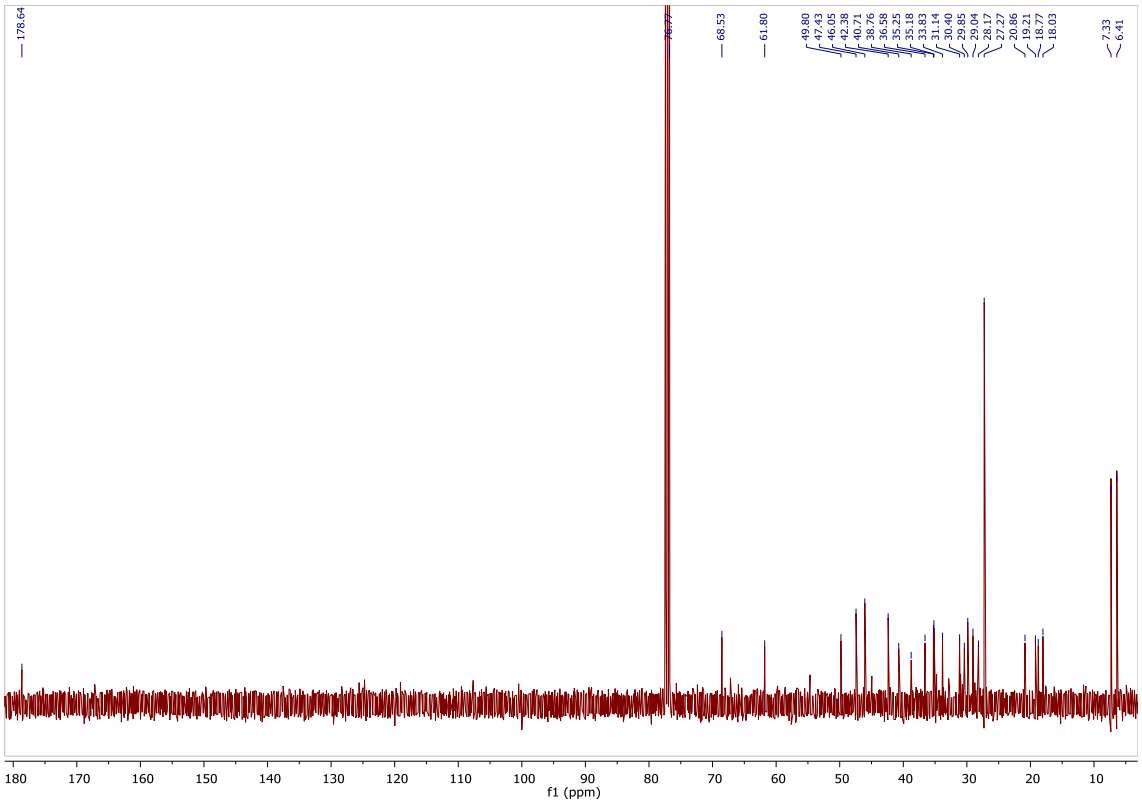

PivO
OH
TESO
HO
199
1.00
1.99
0.99
0.96
3.20
2.95
2.06
9.06
0.90
8.73
6.00
12.25
3.35
6.19
f1 (ppm)

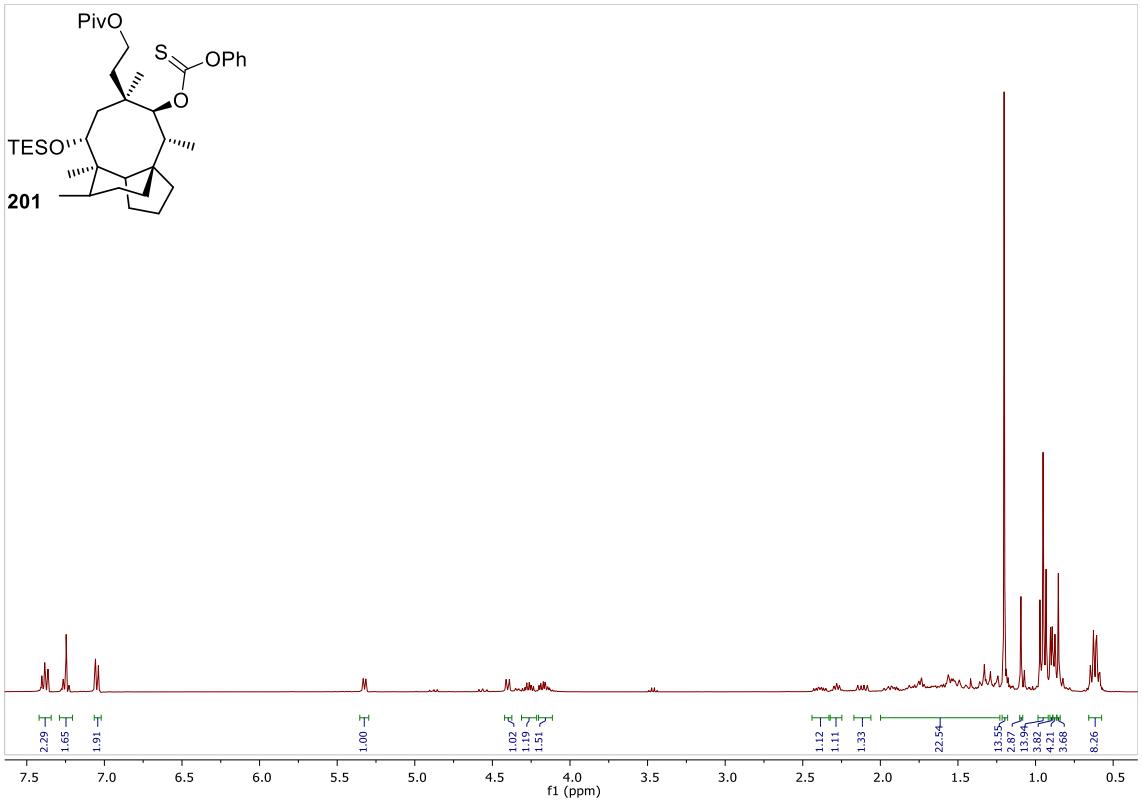

178.59
77.83
76.25
68.50
62.74
51.57
48.42
45.99
43.21
41.20
38.73
37.32
34.74
34.10
33.06
32.81
32.10
28.19
27.29
27.20
18.86
17.55
11.88
7.32
6.35
f1 (ppm)

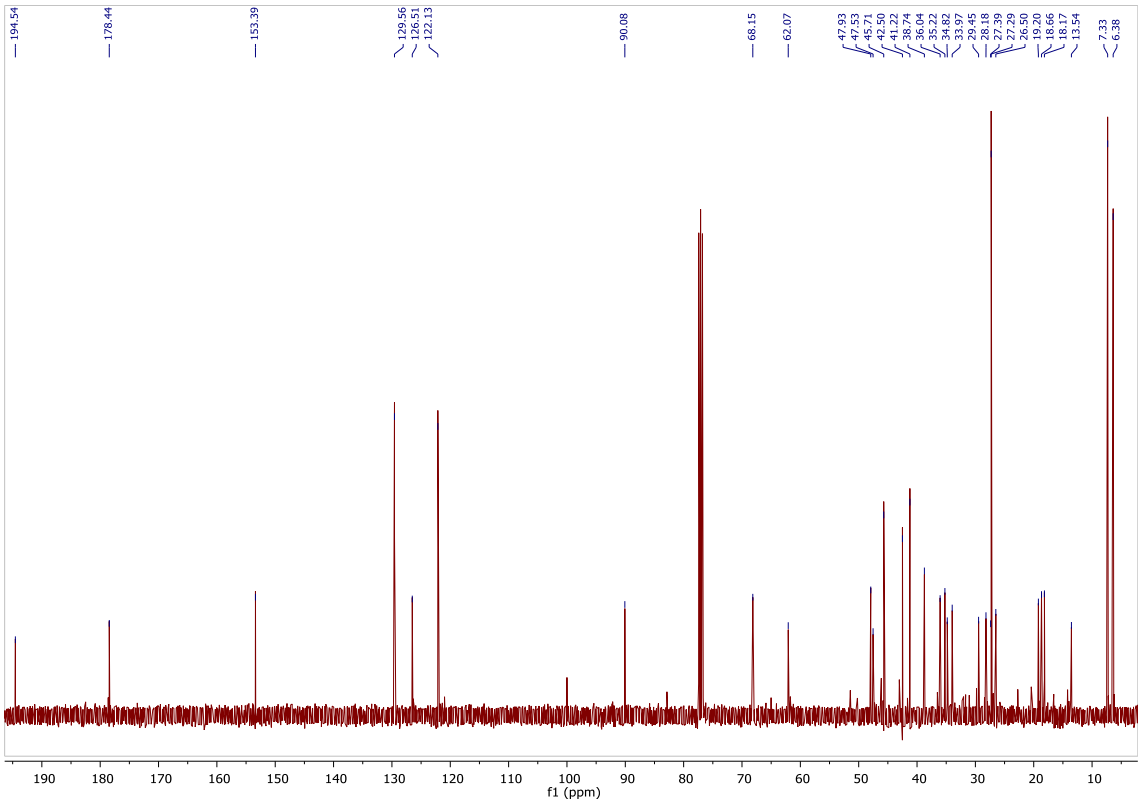

PivO
S
OPh
O
TESO
O
S
OPh
200
4.80
1.97
0.54
4.56
0.48
1.02
0.98
3.27
2.07
3.14
2.01
1.08
10.08
9.65
1.84
3.24
16.54
12.14
6.81
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

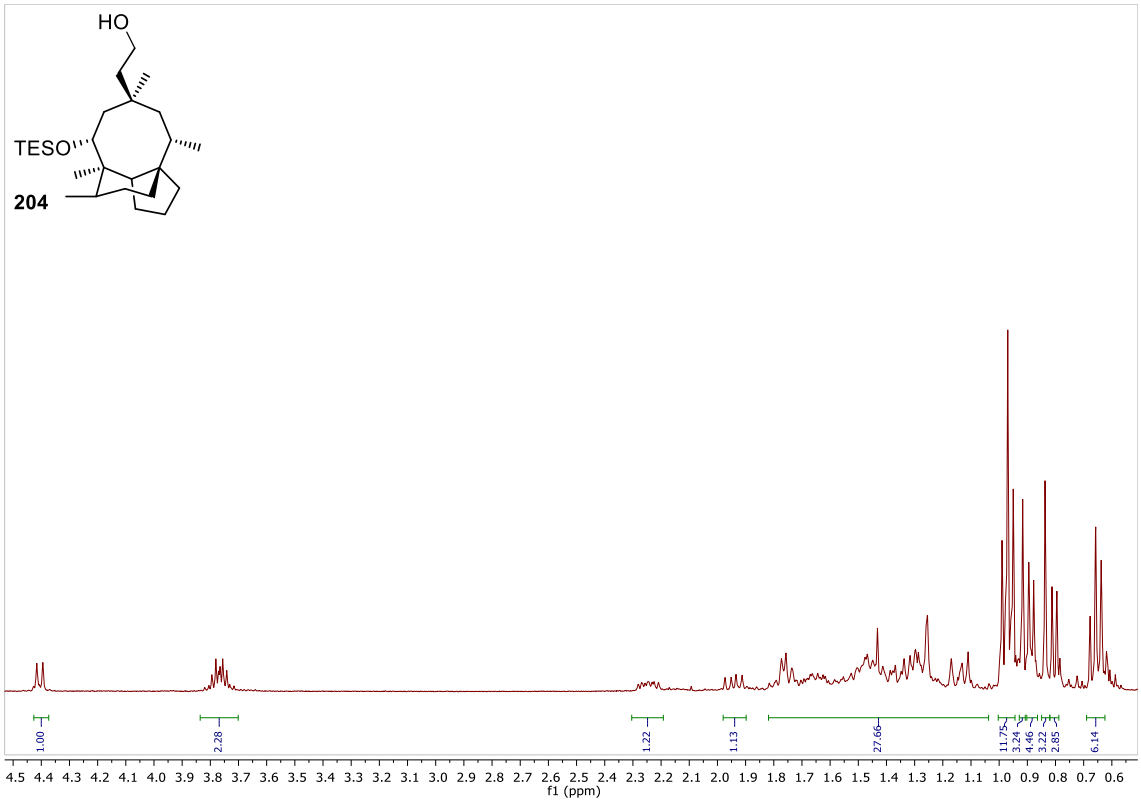

194.77
193.39
178.49
153.35
129.63
126.53
122.05
92.05
89.88
67.91
61.89
51.85
47.95
45.96
42.83
41.37
38.75
36.51
36.00
33.83
33.09
32.36
29.99
28.11
27.28
26.30
18.81
17.63
12.95
7.30
6.36
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

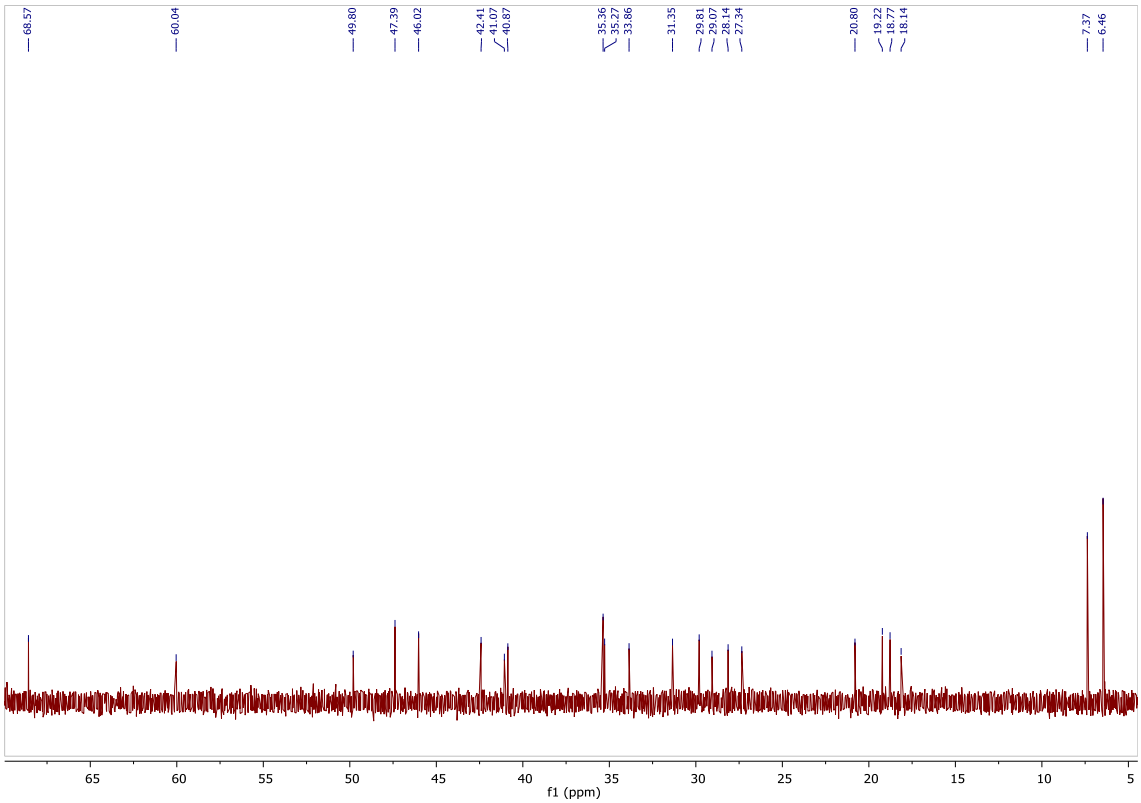

PivO
TESO
202
1.00
2.67
1.92
1.39
1.08
25.31
2.28
12.09
9.28
3.82
3.80
5.96
8.84
f1 (ppm)

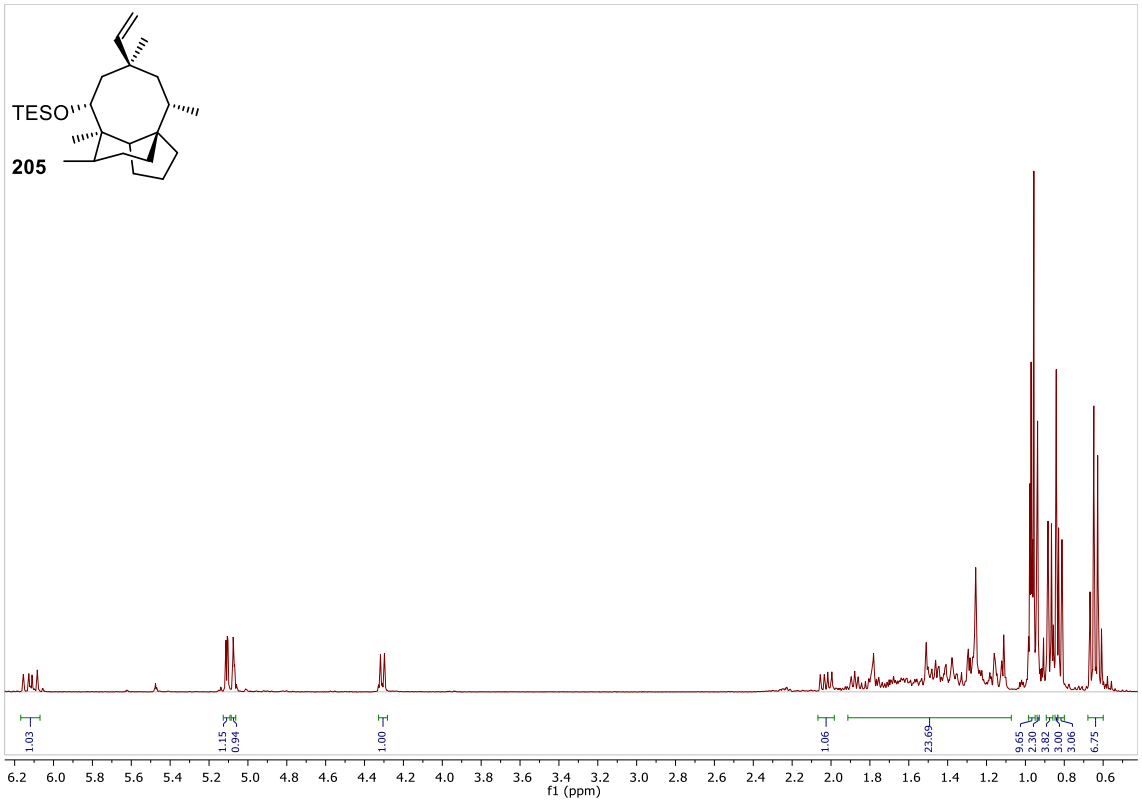

178.64
76.77
68.53
61.80
49.80
47.43
46.05
42.38
40.71
38.76
36.58
35.25
35.18
33.83
31.14
30.40
29.85
29.04
28.17
27.27
20.86
19.21
18.77
18.03
7.33
6.41
f1 (ppm)

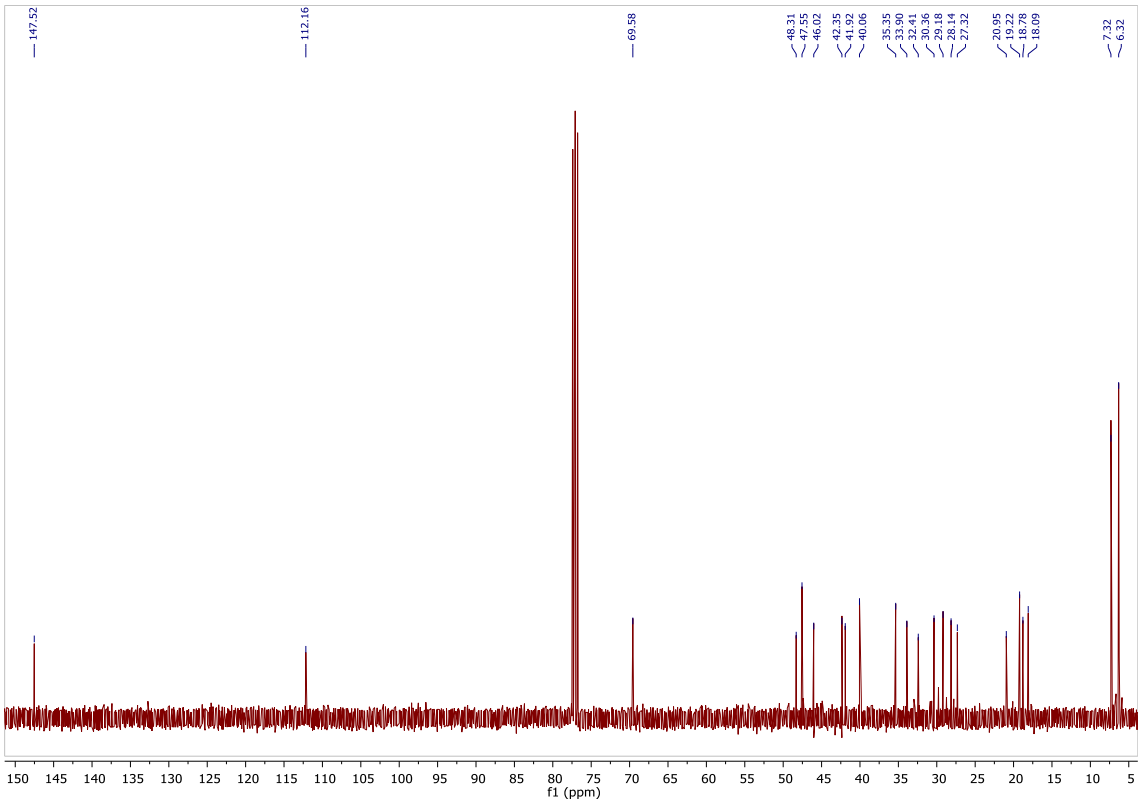

PivO
S
OPh
O
TESO
201
2.29
1.65
1.91
1.00
1.02
1.19
1.51
1.12
1.11
1.33
22.54
13.55
2.87
13.94
3.82
4.21
3.68
8.26
f1 (ppm)

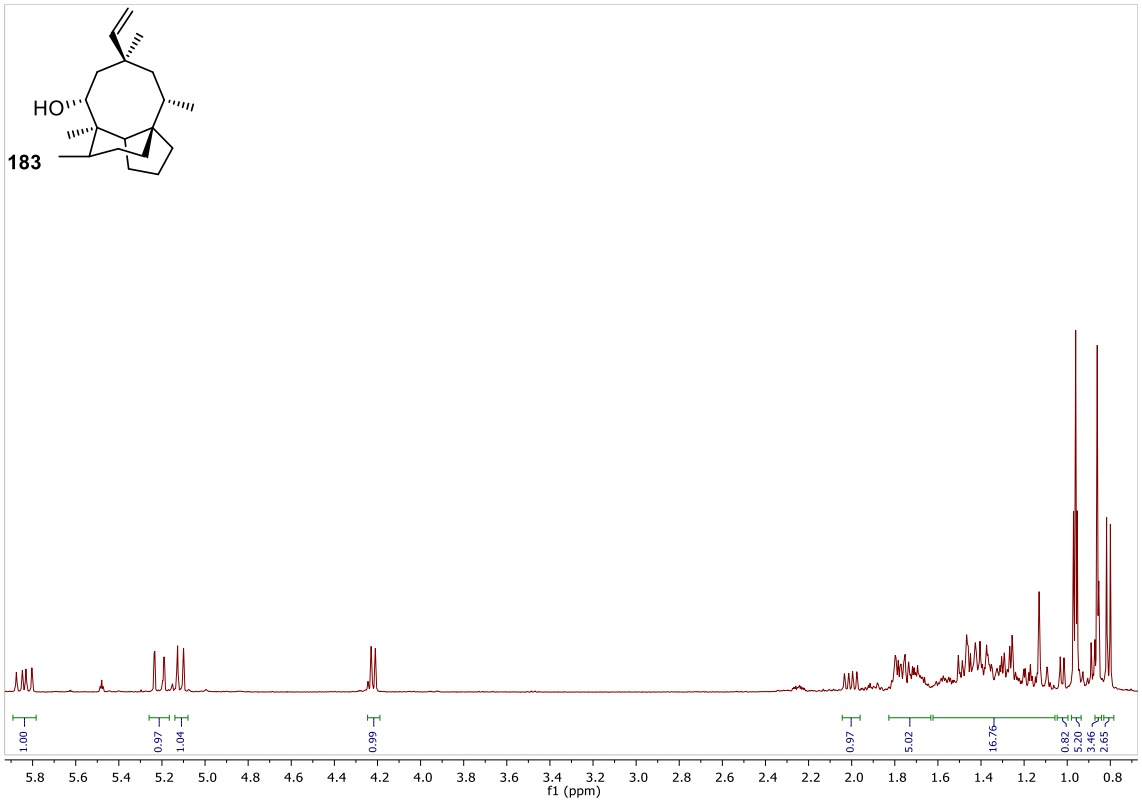

194.54
178.44
153.39
129.56
126.51
122.13
90.08
68.15
62.07
47.93
47.53
45.71
42.50
41.22
38.74
36.64
35.22
34.82
33.97
29.45
28.18
27.39
27.29
26.50
19.20
18.66
18.17
13.54
7.33
6.38
f1 (ppm)

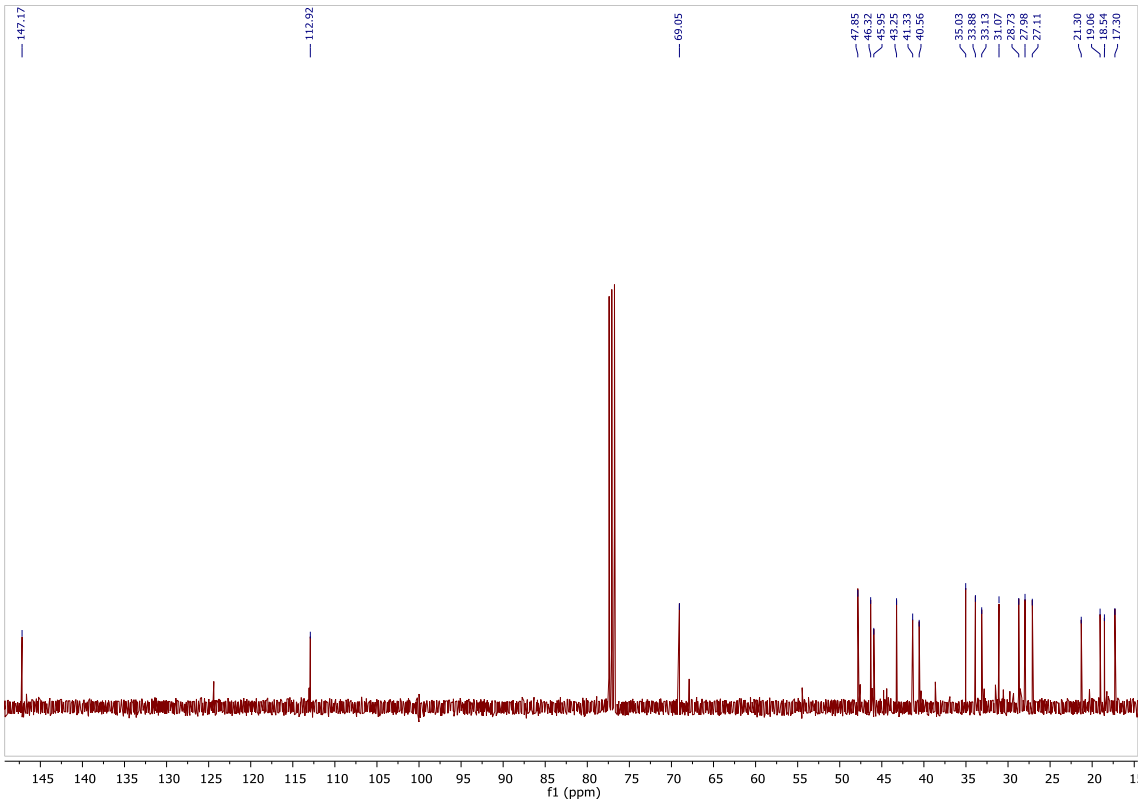

HO
TESO
204
1.00
2.28
1.22
1.13
27.66
11.75
3.24
4.46
3.22
2.85
6.14
f1 (ppm)


68.57
60.04
49.80
47.39
46.02
42.41
41.07
40.87
35.36
35.27
33.86
31.35
29.81
29.07
28.14
27.34
20.80
19.22
18.77
18.14
7.37
6.46
f1 (ppm)


TESO
205
1.03
1.15
0.94
1.00
1.06
23.69
9.65
2.30
3.82
3.00
3.06
6.75
f1 (ppm)


147.52
112.16
69.58
48.31
47.55
46.02
42.35
41.92
40.06
35.35
33.90
32.41
30.36
29.18
28.14
27.32
20.95
19.22
18.78
18.09
7.32
6.32
f1 (ppm)


HO
183
1.00
0.97
1.04
0.99
0.97
5.02
16.76
0.82
5.20
3.46
2.65
f1 (ppm)


147.17
112.92
69.05
47.85
46.32
45.95
43.25
41.33
40.56
35.03
33.88
33.13
31.07
28.73
27.98
27.11
21.30
19.06
18.54
17.30
f1 (ppm)

6. Publications

Heterologous expression reveals the biosynthesis of the antibiotic pleuromutilin and generates bioactive semi-synthetic derivatives F. Alberti, K. Khairudin, **E. Rodriguez-Venegas**, J. A. Davies, P. M. Hayes, C. L. Willis. A. M. Bailey and G. D. Forster, *Nat Commun.*, **2017**, 8, 1831.